2008

EFFECTS OF SURGICALLY INDUCED WEIGHT LOSS ON CARDIOVASCULAR RISK FACTORS

RESULTS FROM THE INTERVENTION STUDY SWEDISH OBESE SUBJECTS

by

C David Sjöström

Göteborg 2000

EFFECTS OF SURGICALLY INDUCED WEIGHT LOSS ON CARDIOVASCULAR RISK FACTORS

RESULTS FROM THE INTERVENTION STUDY SWEDISH OBESE SUBJECTS

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Göteborgs Universitet
kommer att försvaras offentligen i Sahlgrenska Universitetssjukhusets aula,
fredagen den 25 februari 2000, kl 13.00

av
David Sjöström, leg.läkare

Fakultetsopponent:
Professor George A Bray, Pennington Biomedical Research Center,
Baton Rouge, Louisiana, USA

Avhandlingen baseras på följande delarbeten:

I SJÖSTRÖM CD, HÅKANGÅRD AC, LISSNER L, SJÖSTRÖM L.
Body compartment and subcutaneous adipose tissue distribution – risk factor patterns in obese subjects.
Obes Res 1995;3:9-22.

II SJÖSTRÖM CD, LISSNER L, SJÖSTRÖM L.
Relationships between changes in body composition and changes in cardiovascular risk factors: the SOS intervention study.
Obes Res 1997;5:519-530.

III SJÖSTRÖM CD, LISSNER L, WEDEL H, SJÖSTRÖM L.
Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study.
Obes Res 1999;7:477-484.

IV SJÖSTRÖM CD, PELTONEN M, WEDEL H, SJÖSTRÖM L.
Differentiated long-term effects of intentional weight loss on diabetes and hypertension.
Submitted for publication

V SJÖSTRÖM CD, PELTONEN M, SJÖSTRÖM L.
Blood and pulse pressure during long-term weight-loss in the obese: the SOS intervention study.
Submitted for publication

EFFECTS OF SURGICALLY INDUCED WEIGHT LOSS ON CARDIOVASCULAR RISK FACTORS

RESULTS FROM THE INTERVENTION STUDY SWEDISH OBESE SUBJECTS

C David Sjöström M.D., Department of Medicine, Sahlgrenska University Hospital, Göteborg University, Göteborg, Sweden

Aims: To investigate the effects of large maintained weight losses on body composition, adipose tissue distribution and cardiovascular risk factors, i.e. systolic blood pressure, diastolic blood pressure, glucose, insulin, triglycerides, cholesterol, HDL-cholesterol and uric acid.

Methods: Swedish Obese Subjects (SOS) is an ongoing prospective intervention study of obesity. The intervention consists of three types of bariatric surgery. The matched control group receives conventional anti-obesity treatment at primary health care centres. Inclusion criteria for the intervention study are age 37 to 60 years, BMI ≥34 kg/m^2 for men and ≥38 kg/m^2 for women. Ultimately, the two treatment groups will contain 2000 individuals each and the follow-up will be at least 10 years. The use of anthropometric equations, calibrated by means of a multicompartment CT technique, made it possible to estimate lean body mass (LBM), subcutaneous (SAT) and visceral adipose tissue (VAT) masses from weight, height and the sagittal diameter with errors less than 22%.

Results: Two risk patterns were identified. One body composition – risk factor pattern, in which the VAT and SAT masses were positively related to risk factors, while LBM showed negative associations. The other pattern was a subcutaneous adipose tissue distribution – risk factor pattern. SAT in the upper part of the body as estimated by neck girth was positively associated to cardiovascular risk factors, while the reverse was true for a lower body SAT distribution as estimated by thigh girth.

All risk factors except cholesterol were markedly improved two years after bariatric surgery. The two-year incidence of diabetes was reduced 30-fold after a 23% weight loss. In an eight-year perspective, surgically treated patients had lost 16% of their initial body weight while the controls had gained 1%. Surgical treatment reduced the eight-year incidence of diabetes five-fold while it had no effect on the incidence of hypertension. The more pronounced increase in pulse pressure by age seen in the obese could be modified by weight reducing gastric surgery.

Conclusions: Body composition and adipose tissue distribution are closely related to cardiovascular risk factors, also in the severely obese. The metabolic profile is markedly improved by gastric surgery. The effect of surgery on the increasing pulse pressure indicates that the atherosclerotic process may be slowed down by weight reduction.

Key words: Obesity, Controlled clinical trial, Intervention study, Weight loss, Blood pressure, Hypertension, NIDDM, Lipids, Gastroplasty, Gastric Bypass.

ISBN 91-628-3984-5
Göteborg 2000

Printed at Vasastadens Bokbinderi AB, Göteborg
ISBN 91-628-3984-5

EFFECTS OF SURGICALLY INDUCED WEIGHT LOSS ON CARDIOVASCULAR RISK FACTORS

RESULTS FROM THE INTERVENTION STUDY SWEDISH OBESE SUBJECTS

by

C David Sjöström

Department of Medicine,
Sahlgrenska University Hospital,
Göteborg University, Göteborg, Sweden

Göteborg 2000

To

Sofia

ABSTRACT

Aims: To investigate the effects of large maintained weight losses on body composition, adipose tissue distribution and cardiovascular risk factors, i.e. systolic blood pressure, diastolic blood pressure, glucose, insulin, triglycerides, cholesterol, HDL-cholesterol and uric acid.

Methods: Swedish Obese Subjects (SOS) is an ongoing prospective intervention study of obesity. The intervention consists of three types of bariatric surgery. The matched control group receives conventional anti-obesity treatment at 480 primary health care centres. Inclusion criteria for the intervention study are age 37 to 60 years, BMI ≥34 kg/m^2 for men and ≥38 kg/m^2 for women. Ultimately, the two treatment groups will contain 2000 individuals each and the follow-up will be at least 10 years. The use of anthropometric equations, calibrated by means of a multicompartment CT technique, made it possible to estimate lean body mass (LBM), subcutaneous (SAT) and visceral adipose tissue (VAT) masses from weight, height and the sagittal diameter with errors less than 22%.

Results: Two risk patterns were identified. One body composition – risk factor pattern, in which the VAT and SAT masses were positively related to risk factors, while LBM showed negative associations. The other pattern was a SAT distribution – risk factor pattern. SAT in the upper part of the body as estimated by neck girth was positively associated to cardiovascular risk factors, while the reverse was true for a lower body SAT distribution as estimated by thigh girth.

All risk factors except cholesterol were markedly improved two years after bariatric surgery. The two-year incidence of diabetes was reduced 30-fold after a 23% weight loss. In an eight-year perspective, surgically treated patients had lost 16% of their initial body weight while the controls had gained 1%. Surgical treatment reduced the eight-year incidence of diabetes five-fold while it had no effect on the incidence of hypertension. The more pronounced increase in pulse pressure by age seen in the obese could be modified by weight reducing gastric surgery.

Conclusions: Body composition and adipose tissue distribution are closely related to cardiovascular risk factors, also in the severely obese. The metabolic profile is markedly improved by gastric surgery. The effect of surgery on the increasing pulse pressure indicates that the atherosclerotic process may be slowed down by weight reduction.

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I SJÖSTRÖM CD, HÅKANGÅRD AC, LISSNER L, SJÖSTRÖM L.
Body compartment and subcutaneous adipose tissue distribution – risk factor patterns in obese subjects.
Obes Res 1995;3:9-22.

II SJÖSTRÖM CD, LISSNER L, SJÖSTRÖM L.
Relationships between changes in body composition and changes in cardiovascular risk factors: the SOS intervention study.
Obes Res 1997;5:519-530.

III SJÖSTRÖM CD, LISSNER L, WEDEL H, SJÖSTRÖM L.
Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study.
Obes Res 1999;7:477-484.

IV SJÖSTRÖM CD, PELTONEN M, WEDEL H, SJÖSTRÖM L.
Differentiated long-term effects of intentional weight loss on diabetes and hypertension.
Submitted for publication

V SJÖSTRÖM CD, PELTONEN M, SJÖSTRÖM L.
Blood and pulse pressure during long-term weight loss in the obese: the SOS intervention study.
Submitted for publication

TABLE OF CONTENTS

ABBREVIATIONS

AT	Adipose tissue
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CT	Computed tomography
DBP	Diastolic blood pressure
FFA	Free fatty acids
GB	Gastric banding
GBP	Gastric bypass
GLP-1	Glucagon-like peptide 1
HDL	High density lipoprotein
LBM	Lean body mass
LDL	Low density lipoprotein
LPL	Lipoprotein lipase
MRI	Magnetic resonance imaging
NIDDM	Non-insulin-dependent diabetes mellitus
PP	Pulse pressure
SAT	Subcutaneous adipose tissue
SNS	Sympathetic nervous system
SOS	Swedish obese subjects
SBP	Systolic blood pressure
TG	Triglycerides
TRL	Triglyceride rich lipoprotein
VAT	Visceral adipose tissue
VBG	Vertical banded gastroplasty
VLDL	Very low density lipoprotein
WHR	Waist-hip ratio

INTRODUCTION

During the evolution, those individuals have been selected, who had the genetic ability to store energy rapidly in periods of abundance since they had increased chances to survive when food supplies became scarce or lacking. With the fast change of lifestyle in modern society, these survival properties have turned against us as a trap (1, 2). With a better supply of food and an increasingly sedentary way of living, populations all over the world become increasingly obese (3, 4).

Obesity can be described as a condition where the accumulation of excess body fat has reached such proportions that health is jeopardised. Health and well being are not only impaired by the excess fat load per se, but to a large extent by an obesity- associated set of risk factors such as diabetes, hypertension and hyperlipidemia, conditions which all increase the risk of atherosclerosis and subsequent cardiovascular disease. Obesity is also associated with a multitude of other morbidities such as certain cancers, osteoarthrities, gout, sleep apnoea, impaired pulmonary function, psychological and endocrinological disorders(4).

This introductory chapter will give an overview of the epidemiological situation, different types of obesity, cardiovascular risk factors and finally a few words about bariatric surgery, the only anti-obesity treatment with a proven long-term effect on body weight.

1.1 Definition

Obesity is usually defined by means of Quetelet index or the Body Mass Index (BMI)(5) which is the ratio of body weight in kilograms divided by the square of height in meters (kg/m^2). Although not the optimal weight-for-height index for prediction of total body fat(6, 7), BMI still has a good correlation to fat mass(8) as well as morbidity(9) and mortality(10-12). Internationally accepted BMI cut-offs for the definition of underweight, overweight and obesity are given in table 1(4). Many authors use the term overweight for BMI 25-29.9 and define obesity as BMI ≥ 30 kg/m^2.

Table 1. BMI intervals for degree of obesity and cardiovascular risk

Classification	BMI (kg/m^2)	Cardiovascular risk
Underweight	< 18.5	
Normal	18.5-24.9	Average
Overweight	≥25	
Preobese	25-29.9	Increased
Obese class I	30.0-34.9	Moderate
Obese class II	35.0-39.9	Severe
Obese class III	≥40	Very Severe

Adapted from ref.(4)

1.2 Epidemiology

The prevalence of obesity has been increasing rapidly over the last 20 years. There are about 250 million obese adults in the world, and many more overweight. As the increased prevalence is not only seen in the Western world but also in the Third world, WHO has even described the situation as a *global epidemic*(4). Obesity is first emerging in urban middle-aged women. With economic developments, obesity then occurs in men and younger women. In the West where obesity has reached a greater general prevalence, childhood obesity is now rapidly emerging as a new threat(13, 14).

In Sweden 6% of the 18-year old military conscripts were overweight (BMI≥25 kg/m^2) in 1971, whereas in 1995 this figure was 16.3%. The corresponding figures for obesity (BMI ≥30 kg/m^2) had more than tripled from 0.9% to 3.2% over the same period of time(15). Among Swedish adults (16-84 years),the prevalence of obesity (BMI≥30 kg/m^2) is lower than in many other European countries. Still, 12% of Swedish women and 10% of the men are obese (L Lissner, personal communication 1999), whereas figures from Europe range from 10-25% among females and 10-20% among males(16). The prevalence of obesity in the USA has increased more than 30% during the last decade. According to the third NHANES (1988-1994) 20% of the men and 25% of the women were classified as obese(17). More than 50% of the US adults have a BMI exceeding 25 kg/m^2 and thereby they run an increased risk of contracting obesity-related comorbidities(18).

1.3 Some aspects of adipose tissue distribution

Different types of obesity

The relationship between BMI and mortality has been described as J or U shaped(10, 11, 19) or almost linear(20). The observed rise in mortality at low BMI values is to a large extent explained by smoking and history of disease(12, 20, 21).

However, not only body weight or the total amount of fat is of importance for the development of disease, but also the location of the fat depots. This perception was first suggested 50 years ago by Prof. Jean Vague, who constructed the skinfold and extremity circumference based *Fat Distribution Index*(22, 23). He described one android or male pattern of SAT distribution, with a high risk of subsequent metabolic disturbances, such as diabetes and atherosclerosis. This *android* SAT distribution was characterised by a larger accumulation of SAT at the nape of the neck and in the upper limbs as compared to depots in the sacral region and the lower limbs. The SAT depots in the *gynoid* or female type of obesity showed a reversed distribution and were more related to direct mechanical complications of excessive adiposity than to metabolic derangement.

Strangely, the importance of fat distribution did not receive international attention until the early nineteen eighties when cross-sectional associations between risk factors and central or abdominal adiposity appeared in the limelight(24, 25). The preferred anthropometric measurements were now circumferences rather than skinfolds. In prospective studies, the WHR proved to predict cardiovascular morbidity and mortality (26, 27) as well as diabetes(28, 29), also after adjustments for BMI. WHR also seemed to explain the sex difference with respect to incidence of coronary heart disease since incidence-WHR relationships of the two genders had similar slopes and were overlapping(30).

Measurements of visceral obesity

With the increasing interest in VAT, it became important to be able to measure VAT and to find anthropometric measurements from which VAT could be estimated. Multiscan CT techniques for measurement of VAT and SAT volumes were developed(6, 7) and later similar procedures were used for multiple compartmentalisation of the body(31).

For estimation of VAT from anthropometric measurements, three different variables have been evaluated: the WHR, the waist circumference and the recumbent sagittal diameter. All three measurements have been used as indices of *abdominal* or *upper body* obesity. Upper body and abdominal obesity are often used terms. However, none of them makes a distinction between VAT and abdominal SAT. Nevertheless, *abdominal obesity* is closely related to cardiovascular risk factors whether assessed by WHR, waist circumference or the sagittal diameter(32-34).

When estimating the VAT volume from anthropometric measurements, a 'gold standard' is required. Today the gold standard for assessing VAT is the multiscan CT technique(31, 35). With this technique, the precision error is less than 1% for VAT volume determinations(31, 36). VAT area determinations in single CT scans(32) predict the VAT volume with errors being 10-14%(36), which is only marginally better than anthropometric predictions (see below). Thus the VAT area of a single scan is an inappropriate standard when developing anthropometric predictors. This is due to a large inter-individual variation in the VAT distribution within the abdomen(36).

It is evidently important that the anthropometric measurements are collected in a standardised way with fixed anatomical reference points(37). Although recommended, a standing position when taking anthropometric measurements could easily change anatomical relationships in obese persons. In SOS and related studies all anthropometric measurements have been undertaken in the supine position in order to make (regional) comparisons with CT-examinations more meaningful. Measurement of the sagittal diameter should definitely be undertaken in the supine position. The theory behind this is that VAT of a recumbent individual elevates the abdomen, like the filling of a balloon, while the ventrally located abdominal SAT may counteract this increase in sagittal diameter by gravity.

It has been shown that the sagittal diameter differentiates VAT from total AT, while waist circumference seems to be more associated with VAT via its relationship to total AT(36). The intra-abdominal pressure is closer related to the sagittal diameter than waist or WHR(38). The errors when predicting VAT from the supine sagittal diameter range from 15-22%. The corresponding figures for waist and WHR are 22-30% and 26-59%, respectively(36). Thus, the sagittal diameter is superior in estimating the VAT volume. As we will see this does not necessarily imply that the sagittal diameter is superior to waist or WHR as a risk indicator.

Central obesity and risk

As compared to waist and WHR, the sagittal diameter has been closer related to risk factors and mortality in some studies(33, 39) while this has not been the case in other investigations(32). The reason for this may be that waist circumference by its dual relationships adds the negative effects of metabolicly active abdominal SAT(24) and large intra-abdominal VAT depots(40).

The waist circumference is simple to measure and understand and, given its associations with morbidity and mortality, it is thus a suitable measurement for risk evaluations of individuals and populations (34, 41-44). Generally accepted waist circumference cut-off points in relation to risk are shown in table 3. However, these values are specific for Caucasians. Other ethnic groups have different body build and thereby different relationships between waist and risk factors(45, 46). Another reason for a cautious use of these cut-off points is that while very few people would unnecessarily be advised to have weight management, a substantial proportion of those who would need it might be missed(47).

Table 3. Sex specific waist circumferences for increased risk of obesity-associated complications in Caucasians

	Increased	Severe
Men	≥ 94 cm	≥ 102 cm
Women	≥ 80 cm	≥ 88 cm

Adapted from ref.(4)

The WHR is considered to be elevated if ≥0.95 in men and ≥0.80 in women(48).

1.4 Insulin resistance of the metabolic syndrome

During the last 15 years, our knowledge concerning the metabolic syndrome has increased considerably. In general terms, a positive energy balance creating obesity(49) as well as neuroendocrine disturbances elicited by mental stress(50) are causing certain peripheral hormone patterns resulting in insulin resistance. These unfavourable hormone patterns are causing the insulin resistance *directly* in peripheral tissues such as skeletal muscle and liver and *indirectly* via an increased VAT(51) (fig. 1.1).

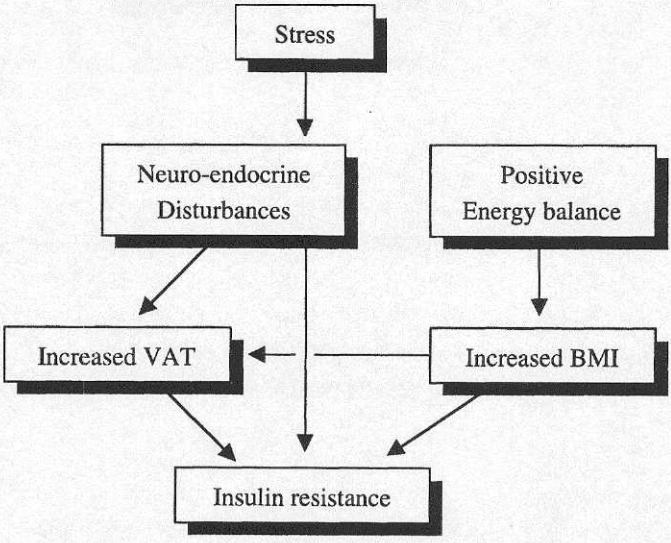

Figure 1.1. Scheme showing the development of insulin resistance in the metabolic syndrome.

Direct mechanisms

HPA-axis

One important direct mechanism for development of insulin resistance is an elevated activity in the limbic-hypothalamic-pituitary-adrenal axis (HPA-axis). This was realised by Vague already in 1956(23). Cortisol induces insulin resistance by increasing liver gluconeogenesis and peripheral amino acid production(52) and by attenuating the insulin mediated peripheral glucose uptake(53). In addition, cortisol has a permissive effect on lipolysis and the resulting increase of FFA will promote insulin resistance via the glucose-fatty acid cycle(54).

Björntorp has suggested that the increased activity of the HPA-axis is part of a civilisation syndrome(55) with stress due to negative psychosocial factors and increased consumption of alcohol and tobacco(50). Accepting an increased WHR as a marker for the metabolic syndrome, experimental evidence for the civilisation syndrome has been

positive associations between the WHR on the one hand, and increased cortisol response to corticotropin (ACTH)(56), increased ACTH and cortisol response to corticotropin-releasing hormone (CRH)(57) and increased cortisol response to mental stress(58), on the other.

Sympathetic nervous system

Several other neuroendocrine disturbances are *directly* involved in the development of insulin resistance. Although the activity of the SNS is decreased in several animal models(59, 60) most human data speak in favour of increased SNS activity in obesity. Thus, human obesity seems to be associated with increased urinary noradrenaline excretion(61, 62), increased muscle sympathetic nerve activity(63, 64) and changes in heart rate variability compatible with increased sympathetic activity and withdrawal of vagal tone(62).

During acute noradrenaline stimulation, beta-2-adrenergic stimulation rapidly elicits insulin resistance in liver and muscle for three to four hours(65). Catecholamines and cAMP rapidly reduce the number of insulin receptors(66), interfere with the ability of insulin to uncover hidden insulin receptors in the cell membrane(67), reduce the number of glucose transporters(68) and interfere with the insulin-mediated docking of transporters in the cell membrane(69). Finally, increased SNS activity may cause increased lipolysis and thus decreased peripheral glucose uptake(54) as well as interference with the insulin–induced inhibition of gluconeogenesis in the liver(70) due to the increased FFA levels. Both these mechanisms will also decrease insulin sensitivity.

Although high SNS activity induces insulin resistance (see above), high insulin levels do also increase the SNS activity as illustrated during hyperinsulinemic euglycemic clamps(64). While basal muscle sympathetic nerve activity is increased two-fold by exogenous insulin in lean subjects the response from elevated basal levels is only 10% in the obese(64), indicating a near maximal insulin-stimulated muscle sympathetic nerve activity in the obese state. A vicious circle thus seems to exist: increased SNS activity causes insulin resistance that maintains high SNS activity.

Androgens

Androgens are differently related to insulin sensitivity in men and women. In women, the metabolic syndrome is characterised by hyperandrogenecity(71) and testosterone

administration causes hyperinsulinemia(72). In men, on the other hand, the metabolic syndrome is associated with low testosterone levels(73) and testosterone substitution results in improved insulin sensitivity(74). However, excessive doses of androgens result in insulin resistance(75). Thus, too low as well as too high levels of testosterone result in insulin resistance in men.

With ageing, human dehydroepiandrosterone sulphate (DHEAS) levels are decreasing and in parallel with this insulin-like growth factor (IGF-1) concentrations are decreasing, plasma tumour necrosis factor alpha (TNF-alpha) levels are increasing and insulin sensitivity is decreasing(76). At least in the Zucker rat, DHEA administration decreases TNF-alpha and improves insulin sensitivity(77).

Some recent observations are not in line with the general picture drawn above. Thus correction of the hyperandrogenecity of the polycystic ovarian syndrome does not result in improved lipids or insulin sensitivity(78). Although testosterone replacement in males with idiopathic hypogonadotrophic hypogonadism improved several risk factors, insulin resistance was not changed(79). None of these conditions may be appropriate models for the metabolic syndrome, but these deviating observations indicate that more research is needed in this field.

Growth hormone

Obesity and especially VAT is negatively related to growth hormone (GH) secretion(80, 81). GH is traditionally looked upon as an insulin-antagonistic hormone(82). Thus, one interpretation is that the metabolic syndrome is associated with insulin resistance in spite of a low GH secretion. A more exciting possibility is that high(82) as well as low(83) GH concentrations are related to insulin resistance. This possibility is supported by the fact that adults with GH deficiency as well as males with abdominal obesity have a reduced insulin sensitivity as determined with clamp technique and that the sensitivity is improved by GH administration(80, 83, 84). In parallel, VAT was reduced and total cholesterol, triglycerides and diastolic blood pressure were improved by GH treatment. Although these results indicate that low GH levels may maintain the disturbances of the metabolic syndrome, they do not prove that low GH values are of primary etiological importance. In fact, the reduced GH secretion of the obese is normalised by weight reduction(85) which indicates that the observed GH disturbances are secondary to obesity and not a pre-existing casual disorder. It should also be observed that not all trials have been able to find improved insulin sensitivity after GH treatment(86).

It has been suggested that insulin resistance is related to a low tissue availability of IGF-1 (as reflected by a low binding protein 1/binding protein 3 ratio) rather than to low IGF-1 levels, at least in hypertensive subjects(87). Interestingly, inhibition of angiotensin converting enzyme does not only improve blood pressure but also insulin resistance and tissue availability of IGF-1. The causal relationships between these observations need further clarification.

Interactions between neuroendocrine axes

One hypothetical possibility is that an increased activity of the HPA-axis will influence all neuroendocrine axes discussed above in a negative direction since it is known that CRH stimulates SNS activity(88), interferes with the gonadotropin-releasing hormone (gnRH) induced release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)(89) and blocks the GH releasing effect of growth hormone releasing hormone (GHRH)(90).

Indirect mechanisms

Most of the hormone disturbances discussed above, which all cause insulin resistance via direct mechanisms on peripheral tissues, are also involved in VAT accumulation. Thus, insulin resistance is also created *indirectly* via VAT accumulation, FFA exposure of the liver, decreased insulin clearance, peripheral hyperinsulinemia and down regulation of insulin receptors.

As compared to fat cells from other depots, visceral adipocytes have a higher density of cytoplasmatic glucocorticoid receptors (GR) and higher concentrations of GRmRNA(91). In the presence of insulin, the cortisol-GR complex binds to nuclear receptors and induces increased LPL activity in AT, both by increasing synthesis after transcription of the LPL gene and by decreasing degradation(92). Normally, testosterone(93) as well as GH(94) are powerful inhibitors of the cortisol-induced increase in LPL activity. Since the developing metabolic syndrome is characterised by low GH in both genders and by low testosterone in men normal inhibition does not occur. All this promotes lipid storage, particularly in VAT with high concentrations of GR.

The lipolytic capacity is also higher in VAT than in other AT depots(95) and thus the FFA turnover is high. This may be related to a higher blood flow(96), a denser

sympathetic nerve supply(91) and/or a diminished antilipolytic effect of insulin(97) in VAT as compared to other AT depots. Since the SNS activity is high during the development of human insulin resistance, the lipolytic activity is certainly kept high.

However, as VAT is growing during the development of the metabolic syndrome lipid storage must be somewhat more active than lipolysis. This may simply be related to a positive energy balance. Furthermore, GH and testosterone(98) are normally intensifying catecholamine-induced lipolysis. Since the two former hormones are low during development of the metabolic syndrome (testosterone low in men only) this might help keeping lipolysis lower than lipid storage.

Although the total FFA release from upper body SAT is much larger than from VAT(99, 100), the VAT depot is thought to be proportionally more important for liver exposure due to the first passage effect of FFA from the portal bed(40). Studies on isolated hepatocytes and rat liver perfused in situ have shown that FFA reduces insulin binding and clearance(101), perhaps via an internalisation of insulin receptors(102). The decreased insulin clearance can be counteracted by drugs reducing mitochondrial FFA oxidation(103). Although human examinations have demonstrated a markedly reduced insulin clearance in subjects with abdominal obesity(104) the decreased clearance does not seem to have been directly coupled to high portal FFA levels in man.

The decreased insulin clearance will cause peripheral hyperinsulinemia leading to down-regulation of insulin receptors and insulin resistance(105).

However, it is very difficult to define the primary cause of insulin resistance once it is established since hyperinsulinemia causes insulin resistance. So far, no insulin studies on secretion, clearance and peripheral resistance have been performed longitudinally both before and during the development of the metabolic syndrome in man.

Another precaution when discussing the pathogenesis of the metabolic syndrome is that several studies discussed above have neither taken the prevailing energy balance nor the general degree of obesity into account. Furthermore, each study has examined only a small piece of a large and complex system. In a recent SOS report, structural equation modelling was used to investigate multivariate relations between anthropometric, metabolic, psychometric, socio-demographic and life style variables cross-sectionally among 1700 males with established obesity(49). BMI was by far the strongest

determinant of VAT and insulin was much closer related to BMI and VAT than to depression, anxiety, physical inactivity and education. Thus, generalised obesity and the underlying positive energy balance should not be underestimated when evaluating the pathogenesis of metabolic disturbances in men with established obesity.

Table 2. Suggested criteria for the metabolic syndrome

The Metabolic Syndrome
Compulsory:
Glucose intolerance/Diabetes and/or Insulin resistance
Plus two of the following:
Blood pressure ≥160/90 mm Hg
Triglycerides ≥ 1.7 and/or HDL < 0.9 (men), <1.0 (women) mmol/L
Microalbuminuria, excretion rate ≥20 μg/min
Central obesity, WHR >0.90 (men) >0.85 (women) and/or BMI ≥30 kg/m^2

Adapted from ref.(106)

A recent WHO expert consultation(106) has recently tried to find criteria for the definition of the metabolic syndrome (Table 2). Considering the complex nature of the metabolic syndrome and the divergent opinions of different investigators, the criteria will most likely be subject of revision.

This chapter has discussed various mechanisms causing insulin resistance. How this resistance is coupled to several other cardiovascular risk factors will be discussed in the next chapter.

1.5 Other cardiovascular risk factors

Non-insulin dependent Diabetes Mellitus

A high relative mortality from diabetes among the obese is well known ever since the Build and Blood Pressure Study 1959(19), and other large studies of overweight and mortality have confirmed this(21, 107). In fact, more than 80% of patients with NIDDM are obese, while only 10% of obese subjects are diabetics(108). NIDDM is intimately related to the degree of overweight(109, 110). The risk of developing NIDDM increases

drastically from BMI 30 kg/m^2 and upwards(110, 111). In addition to overall fatness, measurements of abdominal adiposity are related to the incidence of NIDDM(28, 29, 110). Furthermore, twin studies show that genetic predisposition is important for the development of abnormal glucose tolerance (112). Finally, insulin resistance is also dependent on the degree of physical inactivity(113).

Normally, insulin reduces the circulating levels of glucose by decreasing the hepatic glucose output and by increasing the glucose uptake in muscle and AT. Insulin stimulates the synthesis and the presentation of glucose transport protein (GLUT4) in peripheral tissues. Furthermore, insulin inhibits lipolysis in AT, and thereby lowers the release of FFA and glycerol(114).

One important link between obesity and NIDDM is high levels of FFA(115). The basal rate of lipolysis increases with fat mass(116). High FFA levels induce insulin resistance in liver and the periphery(54) and reduces the hepatic insulin clearance(101). FFA also increases gluconeogenesis in the liver. Insulin production is consequently forced to increase and when the β-cell fails to keep up the production overt NIDDM develops(117). The reason for the failure of the β-cell is not clear but the β-cell secretion of insulin is affected negatively by high glucose and FFA levels (118).

Glucose uptake in the periphery is determined not only by the ability of insulin to stimulate glucose extraction, but also by the rate of substrate delivery, i.e. blood flow(119). High fasting insulin levels(120) as well as a high WHR have been associated with muscle fibres that have low capillary density and reduced aerobic enzyme activity(121, 122). Furthermore, obese subjects have a reduced ability to generate increases in blood flow in response to hyperinsulinemia(123), an observation that may have implications not only for diabetes but also for hypertension.

Apart from FFA secretion, the increased AT in obesity produces other substances with potential, metabolic action. Both leptin(124) and TNF-alpha(125, 126) have been suggested as potential contributors to insulin resistance. Moreover, in women, TNF-alpha was significantly correlated to WHR and insulin levels but not to BMI(126).

Finally, GLP-1 (enteroglucagon) released from terminal ileum in response to increased intraluminal chyme content has anti-NIDDM properties, see Chapter 1.9, Surgical treatment. Thus, subnormal GLP-1 levels may have a diabetic effect.

Hypertension

Since the nineteen-twenties, epidemiological studies have documented a close relationship between high blood pressure and body weight in all age groups and in both sexes(127-129) and estimates of central or abdominal obesity have shown close relationships to blood pressure, independently of BMI(130, 131).

Several mechanisms whereby obesity might cause hypertension have been presented. Although the exact mechanisms are not elucidated, hyperinsulinemia or rather insulin resistance seems to play a central(132, 133) but disputed(134, 135) role. An increased SNS activity(136-138) as well as a disturbed renal function(135) are other pathogenetic mechanisms being discussed. Important argument for a causal relationship between insulin resistance and hypertension is coming from the epidemiological literature. Impaired glucose tolerance predicts the development of hypertension up to 18 years after diagnosis of the impairment(139, 140).

As discussed above (1.4), a high SNS activity is not only causing insulin resistance, but insulin may also activate SNS(64, 136, 137). One observation speaking against insulin as a SNS activator is that patients with insulinoma are usually not hypertensive(141). Since insulin causes vasodilatation in muscles(119), without causing a change in blood pressure, one question has been whether the increased SNS activity is merely a reflex response to the vasodilatation. However the vasodilatation as such is also resistant to insulin in individuals with the metabolic syndrome(119) so there may be no vasodilatation for SNS to react on. The vasodilating action of insulin is thought to be mediated by an endothelial-dependent relaxing factor, such as nitric oxide(142, 143). Indeed, an impairment of the endothelial nitric oxide synthesis is directly related to insulin resistance(144).

Leptin is a more recently discussed candidate for activation of SNS and elevation of blood pressure. In rats, leptin increases blood pressure and the SNS renal signalling(145, 146).

In order to sustain a hypertensive state, an anti-natriuretic shift in kidney function is required(134). How this shift is brought about, within the frames of obesity, is far from clear. The metabolic syndrome-associated insulin resistance seems to be of a selective nature. Despite insulin resistance concerning peripheral glucose uptake, the kidney retains normal sensitivity to the proposed antinatriuretic effect of insulin(147-149). An

increased aldosterone secretion(150, 151) as well as SNS overactivity(137) will further enhance this sodium retention. The increased SNS activity will also cause peripheral vasoconstriction, increased cardiac output as well as activation of the renin-angiotensin-system(152). Insulin could also promote hypertension by augmenting ionic fluxes in vascular smooth muscle cells and thereby increase the sensitivity to pressor amines(152). Furthermore, insulin and growth factors, such as IGF-1, may contribute to the development of hypertension by causing hypertrophy of the vascular wall(153, 154). Structural changes are also seen in the kidneys. Obesity is associated with renal vasodilatation, leading to increased wall stress in the glomeruli. This, accompanied by glucose intolerance and high levels of lipids might promote glomerulosclerosis(135).

An important but often overlooked aspect of hypertension and expanded VAT mass is the direct circulatory effects of increased intra-abdominal pressure. Acutely increased abdominal pressure has profound effects on the circulation(155). Intra-abdominal pressure is directly related to the supine sagittal abdominal diameter (38), which in turn is an indicator of VAT(36). In porcine models it has elegantly been demonstrated how an increased abdominal pressure decreases cardiac output as the venous return is impaired(156). As expected an acutely elevated intra-abdominal pressure decreases urinary output and increases the activity of the renin-angiotensin-aldosterone system(157). Of course, abdominal and intra-thoracic pressure relationships differ between mechanically ventilated swine and spontaneously breathing humans. However, interestingly, an increased abdominal pressure also seems to have direct effects on renal function by increasing renal venous pressure. An increase of the renal vein pressure results in increased plasma renin activity, serum aldosterone and urinary protein leak(158). These changes are consistent with renal alterations in morbid obesity.

As illustrated by the review above, several possible mechanisms for obesity related hypertension have been evaluated without finding a generally applicable model. Therefore, several regulating mechanisms are probably involved, one of which is most likely insulin resistance.

Dyslipidemia

Upper body obesity is linked to elevated fasting TG levels(24, 25) and reduced levels of HDL-cholesterol(159) and high levels of small, dense LDL particles(160), the latter being particular atherogenic(161). Insulin resistance have been coupled to these lipidemic derangements(162-164). The small, dense LDL particles easily undergo

modification and exhibit high affinity to arterial wall proteoglycans. Many lines of evidence indicate that the essential initiating event in early atherosclerosis is the subendothelial retention of cholesterol-rich, atherogenic lipoproteins. (165).

Recently, postprandial lipoprotein metabolism has received a growing interest. Postprandial hypertriglyceridemia has been identified as an independent risk factor for atherosclerosis(166), and TG-rich lipoproteins have been associated with the rupture of atherosclerotic plaques(167, 168).

In the postprandial state, apoB-48 containing chylomicrons are secreted by the intestine(169) while apoB-100 containing VLDL particles are secreted by the liver both during fasting and after food intake. Taken together the postprandial TG-rich lipoproteins are called TRLs. Expressed as number of particles, VLDL constitute about 96% of all TRL particles in the fasting state and this fraction is diminished with only 3-5 %-units 3 and 6 hours postpradially(170). Due to the large size of the chylomicrons they are nevertheless containing 80% of the TG in the TRL fraction in the postprandial phase(171).

In insulin resistant individuals, there is an overproduction of VLDL particles, also in the postprandial state. This can largely be explained by an increased input of FFA-substrate for VLDL production due to the failure of insulin to suppress lipolysis in AT(172), and in particular in VAT. The liver production of *large* VLDL particles is normally reduced by insulin but in type-2 diabetics this mechanism is resistant (173). Thus, this type of insulin resistance may also contribute to the postprandial overproduction of VLDL.

In the fasting state, VLDL is undergoing sequential delipidation by LPL to form LDL. The main destiny of LDL is the hepatic LDL receptors causing internalisation and disassembly of the entire lipoprotein(174). Serial coronary angiographies in some 3500 subjects from more than a dozen studies have demonstrated that lowering of LDL-cholesterol increases regression and inhibits progression of atherosclerotic lesions(175). In spite of aggressive LDL-cholesterol lowering treatment, 20-50% of the treated subjects continue to show progression of atherosclerosis(168). Therefore, factors other than LDL cholesterol must clearly be of importance for the atherosclerotic process.

Postprandially, and in particular in insulin resistant individuals, chylomicrons are competing with VLDL for the same binding sites of LPL in the capillary endothelium of

AT and muscles. LPL is activated by apoC-II which the TRL particles have acquired from HDL as soon as they appear in the circulation(176).The competition between VLDL and chylomicrons results in a delayed lipolysis of these particles(177). The prolonged residence time in the circulation of postprandial TRL permits the cholesteryl ester transfer protein (CETP) to enrich the TRL fraction with cholesteryl esters from HDL and LDL particles(178). Thus cholesterol enriched VLDL and chylomicron remnants are formed that are probably not further delipidated by LPL due to their high cholesterol content (178).

The bulk of TRL remnants are taken up by the liver by using apoE as a ligand and either the LDL receptor or specific remnant receptors(179). However, small VLDL remnants may also be taken up by the arterial wall where they may contribute to the atherosclerotic process(180). ApoC-III, which is a marker for TRL and TRL remnants(181), is related to progression of mild to moderate atherosclerotic lesions(182, 183).

In addition to LDL and TRL remnants, low HDL cholesterol is supposed to play a role in the atherosclerotic process. Nascent forms of HDL are secreted by the liver and intestines and are remodelled into mature forms in the circulation(184). HDL is a class of particles with the density 1.063-1.21 Kg/l. Their core contains mostly cholesteryl esters and triglycerides and their surface contains phospholipids, free cholesterol, and apoA (mainly apoA-1), C and E as well as the enzymes CETP and lecithin-cholesterol acyltransferase (LCAT)(185).

HDL is responsible for the reversed cholesterol transport from peripheral tissues to liver and steroid hormone producing organs. LCAT, on the surface of small HDL particles, converts unesterified cholesterol of peripheral tissues into cholesteryl esters, which are stored in the interior of the HDL particle and transported to the liver and other receiving organs via indirect and direct pathways.

As mentioned above, CEPT transfers cholesteryl esters from HDL and LDL particles to TRL particles thereby creating TRL remnants. This process also results in cholesterol depleted and TG-rich HDL and LDL particles, which are subjected to lipolysis by hepatic TG lipase(186), resulting in an increased number of small dense LDL particles that are particularly atherogenic and in smaller HDL particles that can be more rapidly catabolised through mechanisms that are poorly understood(185). Anyway, the

commonly observed negative correlation between human serum levels of triglycerides and HDL cholesterol is usually explained by the fact that high VLDL levels are causing, not only TRL remnants, but also TG-rich HDL particles which, after lipolysis by the hepatic lipase, are rapidly catabolised. Uptake of TRL remnants and HDL particles by the liver represents the indirect way of cholesterol transport from vessel walls and other peripheral tissues.

In 1996, a scavenger receptor, class B, Type I (SR-BI) was described(187). This receptor, which is expressed in parenchymal liver cells and steroid hormone producing cells in the adrenals, ovaries and testes, represents a direct transport way of cholesterol from the periphery since it is can bind HDL (as well as VLDL and LDL) and transfer cholesterol from the particle to the cell without braking down the lipoprotein(184). In the liver, the cholesterol is mainly used for bile acid and cholesterol production into the bile, and in the other organs for steroid hormone production. In mice, overexpression of the SR-BI receptor dramatically lowers plasma HDL cholesterol, increases bile cholesterol and suppresses atherosclerosis(188) while knockout of SR-BI has opposite effects(189).

It has been known that overexpression of apoA-I or weekly injections of purified apoA-I has inhibitory effects of the initiation and progression of atherosclerotic lesions in cholesterol-fed rabbits(190, 191). Recently, it was reported for the first time that liver-directed viral gene transfer of human apoA-I resulted in significant regression of pre-existing atherosclerotic lesions in LDL receptor-deficient mice(192).

The new knowledge on overexpression of apoA-I and the HDL SR-BI receptor has not yet been transferred to human interventions. When this occurs, the established negative correlations between HDL and atherosclerosis or between HDL and triglycerides will not necessarily be seen. Today, however, older studies such the Helsinki Heart Study(193) clearly support the idea that HDL cholesterol levels are negatively related to atherosclerosis. In the Helsinki Heart Study, it was estimated that for every 1% increase in HDL cholesterol, there was a 3% decrease in the risk of having a coronary event. The recent Veterans Affairs HDL Cholesterol Intervention Trial has confirmed results from earlier studies and shown that elevation of HDL cholesterol reduces the incidence of coronary events in patients with normal LDL levels(194).

As reviewed above, visceral obesity and insulin resistance are related to elevated VLDL and dense LDL levels and to reduced HDL levels. These circumstances clearly indicate that weight reduction is important in obese subjects.

Hyperuricaemia

The association between hyperuricaemia and cardiovascular disease has been recognised for about 40 years(195), when it was discovered that half of the patients with gout died of either coronary heart disease, congestive cardiac failure or intracranial haemorrhage. Later, the association with coronary heart disease was confirmed longitudinally(196). The association between BMI, components of the metabolic syndrome and uric acid is now well established(197). Consequently, the association between uric acid and morbidity has usually been regarded predominantly as a result of the covariation with adiposity and the metabolic syndrome. Insulin seems to decrease the renal excretion of uric acid together with sodium, also in insulin resistant hypertensive individuals(149).

Uric acid is the final product of adenine degradation and is generated by the enzyme xanthine oxidase. There is an increased availability of uric acid precursors and activation of xanthine oxidase during cell break down and in conditions of global or regional hypoxia(198-200). Xanthine oxidase releases oxygen-derived free radicals(201). This is a most interesting finding as it provides a theoretical link between vascular endothelial injury and urate overproduction(202). Indeed, allopurinol has been shown to protect the myocardium against hypoxic injury in patients undergoing heart operations(203). Furthermore, the xanthine oxidase derived reactive oxygen species increase the expression of adhesion molecules by leukocytes(204), a prerequisite for their adhesion and accumulation in endothelial lesions. Free radicals may also be involved in premature rupturing of atherosclerotic plaques(205). The generation of nitric oxide, a potent endothelial-dependent vasodilator, increases under conditions where superoxide generation increases. In fact, nitric oxide inactivates the xanthine-oxidising enzymes(206). Unfortunately, impaired nitric oxide synthesis is linked to a cardinal feature of the metabolic syndrome, i.e. insulin resistance(143, 144).

In short, hyperuricaemia may be a marker of a generalised endothelial dysfunction rather than a causal factor. It is a potent predictor of mortality in patients with chronic heart failure(207).

1.6 Weight loss, morbidity and mortality

Numerous studies have shown beneficial effects of weight loss on dyslipidemia(208), hypertension(209) and NIDDM(210). Today there is a generally accepted idea that a 5 to 10 percent weight loss is sufficient for improvements in cardiovascular risk factors(211, 212). Thus, an overwhelming literature suggests beneficial effects of weight loss on cardiovascular risk factors. Consequently, one would expect these positive effects to be reflected in epidemiological mortality data. Surprisingly, it is difficult to find any support for mortality reducing effects of weight loss. In fact, weight loss rather seems to increase mortality rates(213). In NHANES I, this was true also for cardiovascular death among initially overweight men and women. This relationship was maintained also after exclusion of deaths occurring during the first 8 years and after controlling for smoking(214). Other studies have shown the lowest mortality in weight stable individuals while increased risk is associated with weight gain as well as with weight loss among men(215) and women(216).

Lack of evidence for beneficial effects of weight loss on cardiovascular or all-cause mortality has generally been regarded as a failure in controlling for confounders(213). Furthermore, the effectiveness of excluding early death as a means of controlling for confounding by occult disease has been questioned(217). Considering the difficulties in losing weight voluntarily(218), it is not remarkable that more than half of weight losses exceeding 9 kg were not intentional, as reported from a large study of middle aged women(219). In fact, the volition of weight loss might be one key to the understanding of the contradictory association between weight change and mortality. Unfortunately, only data from the American cancer society study has permitted some sort of corrections for unintentional weight loss. In obese women with obesity associated co-morbidities intentional weight loss was associated with reduced mortality(220). However, results were neither totally consistent in women without co-morbidities(220) nor in men with or without co-morbidities(221).

Another interesting hypothesis is that loss of LBM would be associated with increased mortality while loss of fat is related to decreased mortality. Available investigations preoccupied with changes in weight or BMI are missing this distinction(222).

A third explanation for the fact that weight loss has beneficial effects on risk factors but not on mortality might be that most risk factor studies are shorter than one year (211) while mortality has usually been studied over ten years or more. Thus, it is not known if

initially, beneficial effects on risk factors are preserved long-term in still obese individuals with a maintained weight loss. Barakat has suggested that insulin sensitivity is connected to a threshold around BMI 30 kg/m^2 above which weight reductions would not improve insulin sensitivity(223). Similar suggestions have recently been presented by others(224). A recent finding also calling for more long-term interventions is the relapse in LDL and total cholesterol after one year despite no observed weight relapse in a group of weight reduced obese women(225). Orlistat trials, which result in weight losses of about 4 to 6 percent in the placebo group and 8–10% in the orlistat group over 2 years, have demonstrated that the weight loss of the placebo group is not enough to keep any risk factors down over 2 years while 8-10% weight reduction improves all risk factors over the same period of time (226).

Little is known about risk factor improvements after 5 to 10 years of maintained intentional weight loss. Short follow-ups and small weight losses in risk factor studies are not surprising considering the disappointing results of traditional dietary weight-loss regimens. After one year 75% of patients participating in dietary programs have regained most of their lost weight(218). The adherence to behaviour modification and exercise programs aiming at counteracting the weight regain is also declining fast(218).

For a better understanding of the weight loss - risk factor - mortality controversy, controlled intervention studies with large and maintained, intentional weigh losses over prolonged periods of time (5-10 years) are needed. At present, the SOS study is the only ongoing study that has been designed to study these problems.

1.7 Surgical treatment

Traditionally, two factors of importance for weight control have been considered in the surgical treatment of obesity: 1) restriction of food intake, and 2) malabsorption of energy. More recently, 3) an increased release of GLP-1 has been included among weight reducing and anti-diabetic mechanisms.

Intestinal operations

These operations are causing malabsorption. The *jejunocolic shunt operations* were introduced in 1963 by Payne(227). These operations were very effective, but associated with severe diarrhoea and hepatic failure and were therefore soon abandoned. In contrast, the *jejuno-ileal bypass* (JIB), introduced in 1976(228) has been widely used.

Jejunum is divided 37.5 cm from the ligament of Trietz. The proximal end is anastomosed to ileum 10-12 cm from the ileo-coecal valve while the distal segment of the divided jejunum is closed resulting in a blind loop. JIB results in large weight reductions (30-50 kg) but also in a number of late side effects including immunological disorders and liver damage(229). For these reasons, most authorities in the field do not recommend JIB.

Gastric operations

Gastric operations have a restrictive mood of action. Several variants of so called *horizontal gastroplasties*(230, 231), including that described by Gomez(232) turned out to be long-term inefficient due to stoma dilatation and pouch enlargement. These techniques are not in use today.

Gastric banding(233) was introduced in the early 1980's. A silicon band is strapped around the upper part of the stomach resulting in an hourglass-shaped ventricle with a small (20 ml) upper pouch. Later this technique has changed into a *variable banding* method achieved by means of a balloon on the gastric side of the silicon band. The balloon is connected with a subcutaneous port or reservoir with a self-sealing membrane(234, 235). The size of the stoma can be changed by adding or removing fluid from the system by means of a percutaneous puncture of the membrane (fig. 1.2). Nowadays, this operation is often performed laparoscopically(236) and it usually results in a 20–30% weight loss.

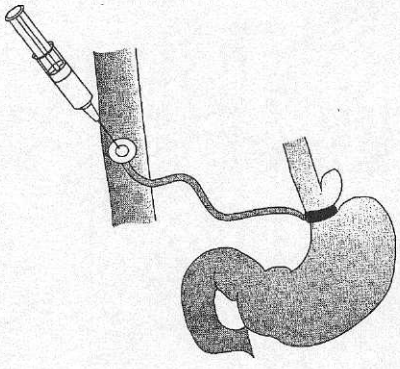

Figure 1.2. Gastric banding, with permission ref.(240)

Vertical banded gastroplasty was introduced 1980 by Mason(237) (fig. 1.3). A channel is created through the ventricle walls approximately 2 cm from the lesser curvature and 4-5 cm below the angle of His. The front and back walls of the stomach are then stapled together from the channel up to the angel of His. Finally, a polypropylene strip (1.5 cm wide) is brought through the channel and around the lesser curvature and sutured to itself so that its circumference is 5 cm. Although less common than for banding, VBG can also be performed laparoscopically(238). The weight loss with VBG is in the order of 20-30%(239).

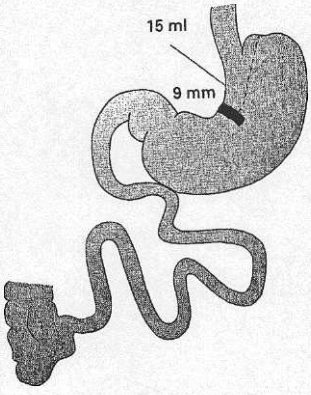

Figure 1.3. Vertical banded gastroplasty, with permission ref.(240)

Combined gastric and intestinal operations

With these techniques restriction as well as malabsorption are achieved.

The original *gastric bypass* technique was described by Mason in 1967(241). Later it has been modified in several steps(242). Nowadays, GBP is usually characterised by a pouch along the lesser curvature and a so-called Roux-en-Y arrangement of jejunum (fig. 1.4). Jejunum is divided 45 cm from the ligament of Trietz and the distal segment is brought up retrocolically and antegastrically for the lesser curvature gastro-jejunal anastomosis to the pouch. The proximal segment of the divided jejunum is used for an

end-to-side jejuno-jejuno-stomy 35-60 cm from the pouch. GBP usually results in 30–50% weight loss(239). Laparoscopic techniques for GBP have recently been developed by Lönroth(243, 244).

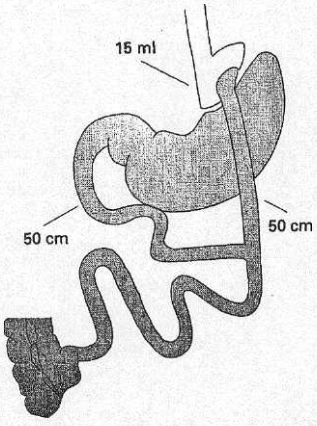

Figure 1.4. Gastric bypass, with permission ref.(240)

The *biliopancreatic diversion* was introduced by Scopinaro in the 1970's(245). This is an extensive operation causing close to normalisation of body weight but also negative nitrogen and calcium balance as well as symptoms of deficiency of fat soluble vitamins in a substantial fraction (10-15%) of the treated patients. Seventy-five percent of the distal stomach is removed and the remaining proximal stomach and the duodenal stump are closed. Ileum is divided 250 cm from the ileocecal valve and the distal segment (the alimentary limb) is anastomosed to the remaining stomach. The proximal segment of the divided ileum (the biliopancreatic limb) is anastomosed to the side of terminal ileum 50 cm from the ileocecal valve. Scopinaro has reported on results from 2241 patients operated over 21 years(246). The operative mortality was low, 0.5%, and the patients lost 75% of their initial excess body weight.

The importance of GLP-1

As mentioned in chapter 1.5, GLP-1 is released from terminal ileum in response to increased intraluminal chyme content. It has weight reducing and anti-NIDDM properties by inhibiting pancreatic glucagon secretion, stimulating insulin secretion,

prolonging gastric emptying and decreasing intestinal motility(247). This is of particular interest in bariatric operations where the pyloric muscle is bypassed. The bypass causes a rapid movement of gastric contents into the small bowel and thereby an increased release of GLP-1. Increased GLP-1 responses to food has been documented after JIB, GBP as well as biliopancreatic diversion(247). Furthermore, data suggest that GLP-1 is responsible for the dumping seen in gastrectomised patients(248). Finally, GLP-1 has been suggested as an inhibitor of appetite and GLP-1-receptors have been demonstrated outside the blood-brain barrier in the subfornical organ and in area postrema(249). As compared to entirely gastric operations, the increased GLP-1 responses seen after GBP, JIB and biliopancreatic diversion thus seem to contribute to the larger weight reduction and the more pronounced effects on NIDDM seen with these techniques.

1.8 Conventional as compared to surgical treatment

Four studies have been designed to compare conventionally and surgically induced weight loss. One of these is the SOS study, see Results.

In the *Danish Obesity Study* 202 patients were randomised to jejunoileal bypass (JIB) or diet(250). After two years, the weight loss was 43 kg in the JIB group and 6 kg in the diet group. In the surgical group, quality of life as well as blood pressure was markedly improved but numerous complications were also observed, some of which were serious.

Two(251) and five-year(252) results have been reported from another Danish study. Sixty patients were randomised to horizontal gastroplasty (HP) or a very low calorie diet (VLCD) followed by traditional dieting. After 2 years, the weight loss was 31 kg in the HP group and 8 kg in the VLCD group. At 5 years, weight losses were not reported while *cumulated success rate* defined as more than 10 kg maintained weight loss was 16% in the HP group and 3% in the VLCD/diet group. As discussed above the HP technique is not used nowadays due to the poor long-term results.

In an American, prospective, non-randomised, non-matched study, 201 patients were treated with GBP and 161 patients with VLCD followed by weekly diet counselling for 18 months(253). The patients were followed for 2 to 6 years and at the latter occasion, 30% of the patients were available. Initial, minimum and 6-year BMIs were 49.3, 31.8 and 33.7 kg/m^2 in the GBP group and 41.2, 32.1 and 38.5 kg/m^2 in the VLCD/diet group. In spite of a much higher initial BMI, the GBP group thus achieved a lower

minimum BMI that was largely maintained. Only 11% of the lost weight were regained after 6 years. The VLCD group had a very satisfying initial weight loss but had regained 70% of the lost weight after 6 years.

The conventional treatment results of the three studies discussed above are representative for or moderately better than conventional results in general, achieved by teams specialised in the treatment of obesity. However, the great majority of all obese patients are thrown upon the resources of the primary health care. Until the SOS study was started, no results from obesity treatment in primary health care settings were available.

AIMS OF THIS THESIS

The SOS study has been undertaken at 480 primary health care centres and 25 surgical departments. These circumstances made it impossible to perform advanced examinations such as clamp studies, postprandial trials, advanced body composition examinations or measurements of energy expenditure. Instead, SOS is relying on simple anthropometry, basal biochemistry at 0, 2 and 10 years, comprehensive questionnaires and a strict study administration.

The overall aim of this thesis, dealing with severely obese subjects, was to evaluate the effects of large sustained, intentional weight losses on body composition and the following cardiovascular risk factors: SBP, DBP, Glucose, Insulin, Cholesterol, HDL, TG and Uric acid.

More specifically, the goals were:

- To separate the effects of VAT and SAT mass from those of SAT distribution - on risk factors (papers I and II).
- To study the cross-sectional relationships between AT distribution, body composition and risk factors (paper I).
- To describe the relationships between changes in body weight, body composition and risk factors (paper II).
- To determine the reduction in the two-year incidences of hypertension, diabetes and lipid disturbances after bariatric surgery (paper III).
- To examine the eight-year effects of a sustained, intentional weight loss on diabetes and hypertension (paper IV).
- To study weight, weight change and ageing as predictors of the long-term relapse in blood pressure, occurring in spite of a large maintained intentional weight loss (paper V).
- To examine the effects of weight loss on the development of pulse pressure (paper V).

METHODS

3.1 The SOS study

The Swedish Obese Subjects study(254) was started in 1987 as a pilot study. Since 1993, it is a countrywide investigation involving 480 primary health care centres and 25 surgical departments throughout Sweden. It consists of a registry and an intervention study.

Registry study

The registry study is a health examination of obese individuals undertaken by 480 primary health care centres in Sweden. Between six and ten thousand obese patients will be included.

The primary aims of the registry study are: a) to describe the obese patient with respect to body composition and AT distribution, metabolic aberrations, dietary habits, psychological and socio-economic variables, b) to investigate the dependency of obesity on genetic and cultural factors, c) to constitute a recruitment base for the intervention study.

Patients are recruited into the registry study through advertisements in newspapers, radio and television. Inclusion criteria are age 37-57 years, BMI $\geq$ 34 for men and BMI $\geq$ 38 kg/m^2 for women, according to a height-weight table. The patients must also have completed a number of questionnaires before a registry health examination with blood sampling is undertaken. The questionnaires delineate weight development in the patient and his family, dietary habits, diseases, medication, utilisation of medical care, ethnic origin, education, socio-economic status, sleep patterns, physical activity and psychological status.

Intervention study

From the registry, eligible patients are recruited into an intervention study. The primary aims of the intervention study are to investigate the effects of intentional weight loss on mortality and morbidity. Secondary aims are to examine how large weight losses that are needed in order to ameliorate the disturbed cardiovascular risk factor patterns seen

in the obese and to follow the development of body composition, socio-economic and psychological variables longitudinally.

Inclusion criteria for the intervention study are age 37-60 (three year higher upper limit than in the registry study) and BMI ≥ 38 for women and BMI ≥ 34 kg/m^2 for men. Severe illness, abuse of alcohol or drugs and previous bariatric surgery were reasons for exclusion while diabetes, hypertension and previously experienced (not last 6 months) myocardial infarction were not.

The SOS intervention study offers two treatment arms: one conventional and one surgical. It was neither feasible nor scientifically desirable to introduce a standardised treatment for the controls followed at 480 primary health care centres. Instead, SOS controls receive the customary obesity treatment of the site to which they belong. The intervention within SOS consists of three types of gastric surgery performed at 25 surgical departments. The operation types are VBG, GB and GBP(255) (fig. 1.2-4).

The SOS intervention study is not randomised as the Ethic committees did not approve of such design considering the high postoperative mortality in the early eighties (1 to 5%). Therefore, a matched controlled design was chosen. When selecting matches for the surgically treated patients from potential controls of the registry a computerised matching program is taking the following 18 variables into account: sex (absolute match), age, weight, height, waist circumference, hip circumference, systolic blood pressure, s-cholesterol, s-triglycerides, smoking, diabetes, pre/post menopausal state among women, four psychosocial variables known to be associated with mortality (current health, availability of social interaction, availability of attachment, stressful life events) and two personality traits related to treatment preferences (psychastenia, monotony avoidance). The algorithm of the computer program chooses controls in order to move the two group means of all matching variables as close to each other as possible. A surgically treated patient and its matched control started the intervention on the operation day of the former.

The two treatments arms will contain 2000 subjects each and the follow up period will be at least 10 years. The patients undergo health examinations and fill out questionnaires at certain intervals. These are year: 0, 0.5, 1, 2, 3, 4, 6, 8, and 10. Blood samples are collected for centralised analysis at 0, 2 and 10 years.

3.2 Study groups

The study groups in paper I to V are all derived from the SOS study with the above mentioned inclusion criteria. An overview of the number of participants is shown in table 1. *No. Used* denotes the actual number of participants used in the calculations and *No. Total* signifies the number of participants that would have been available had there been no dropouts.

Table 1. Study designs and number of participants in paper I-V.

Paper	Study design		No.Used	No.Total
I	Cross-sectional	Registry	2450	2450
II	Longitudinal 2 yr.	Intervention	842	948
III	Longitudinal 2 yr.	Intervention	1479	1690
IV	Longitudinal 8 yr.	Intervention	483	692
V	Longitudinal 3-10 yr.	Intervention	2188	2750

All participants were obese. At the start of the intervention mean BMI for men was 40±5 kg/m^2 and for women 42±5 kg/m^2. Mean age was 48±6 years for both genders.

In paper I data from an independent examination of 203 men and women, with BMI 35.5±5.0 kg/m^2 (range 28 to 50) and age 43±12 years were used to investigate the relationship between height, LBM, and total body potassium.

3.3 Anthropometry

Involved staff members of the centres were trained in measuring the anthropometric variables at the start of the study and at annual reinforcing meetings.

The following anthropometric measurements have been used: Body weight to the nearest 0,1 kg without shoes in indoor clothing. Body height without shoes to the nearest 0.01m. Sagittal diameter in cm was measured by means of a carpenter's spirit level and a ruler. The patients were examined in the recumbent position on a firm examination table. The spirit level was placed 90 degrees to the length axis of the body over the abdomen at the level of the iliac crest. The sagittal (antero-posterior) diameter

was the vertical distance from the examination table up to the horizontal level as measured with a ruler.

Four trunk and three limb circumferences were measured in the recumbent position: *neck circumference,* shortest possible circumference without any compression of tissues; *upper waist,* at the level midway between proc. xiphoideus and a line connecting the most caudal part of the lateral costal arch on the left and the right side; *waist,* at the level midway between the most caudal part of the lateral costal arch and the iliac crest; *hip,* at the symphysis-trochanter femoris level; *upper arm,* on the right arm, midway between apex axillae and the cubital fold; *thigh,* on the right leg, just below the gluteal fold; *calf,* midway between the centre of the patella and the medial malleol. Clothes were removed from the measured regions.

3.4 Blood pressure

SBP and Korotkoff phase 5 DBP were measured after 15 minutes in a supine position. The last five of these 15 minutes the patients spent in complete rest. Cuff width and upper arm circumference were recorded in each individual case. The blood pressures were adjusted for any incongruities in these measurements before analysis(256).

3.5 Biochemistry

Serum, EDTA plasma as well as heparin fluoride blood and serum were sampled at the collaborating centres after an overnight fast.

Table 2. Biochemical analyses

Analysis	Method	CV (%)
B-Glucose	Enzymatic	4
S-Insulin	Radio immuno assay	10
S-Cholesterol	Enzymatic	3
S-HDL	Precipitation	5
S-TG	Enzymatic	4
S-Uric acid	Enzymatic	3

The samples were then sent by overnight mail, to the Central Laboratory at Sahlgrenska University Hospital, Göteborg, for standard biochemical analyses. The laboratory is accredited according to European norm 45 001. Table 2 shows the biochemical analysis with variation coefficients used in paper I-III.

3.6 Questionnaires

Extensive information on patients was collected through self-administered questionnaires. Information on medication, hypertension, diabetes, smoking, previously experienced myocardial infarction, physical activity, energy- and alcohol intake was used.

The questions about physical activity during work and leisure-time are dividing the physical activity in four levels. These questions were constructed 30 years ago(257) and have been used in a large number of investigations(258-260).

The food-questionnaire has been validated in obese as well as in non-obese(261) against estimated(261) as well as measured(260) 24-hour energy expenditure.

3.7 Body composition

Total body potassium

Radiation from the naturally occurring isotope ^{40}K was measured in a carefully shielded whole-body gamma counter with a precision of 2.5%(262). Since ^{40}K constitutes a known fraction of all potassium, TBK can be estimated. Furthermore, as 99% of TBK is located intracellularly and as the potassium content of FFM and LBM (i.e. the non-AT) has been estimated in both genders(6, 7, 263), it is possible to calculate the amount of FFM (kg) and LBM (kg) from TBK.

CT-calibrated anthropometric equations

LBM, SAT and VAT masses were estimated by using CT calibrated, sex specific, anthropometric equations(36, 264, 265). The equations are based on the recumbent sagittal abdominal diameter (D, cm), weight (W, kg) and height (H, m). The W/H ratio is the weight for height index being optimally related to total AT both in women(6) and in men(7). The sagittal diameter, measured as described above, is closer related to VAT than either waist circumference or WHR(36, 264).

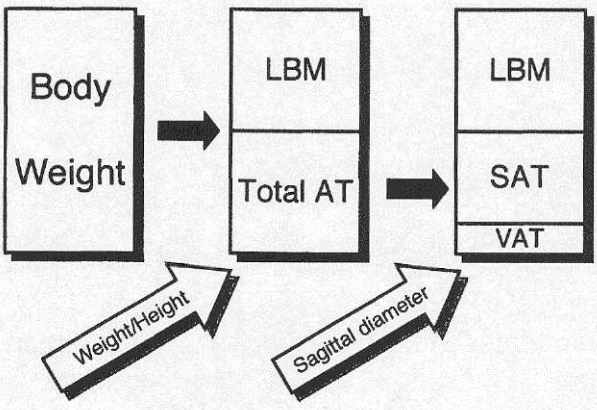

Figure 3.1. The 3-Compartment body composition model used in this thesis. Body weight is measured. Total AT is obtained from weight/height and VAT from the sagittal diameter. Remaining compartments are calculated by difference.

Estimation of total and visceral adipose tissue

Males:	Total AT, litres =1,36 x W/H -42,0
	VAT, litres =0,731 x D -11,5
Females:	Total AT, litres =1,61 x W/H -38,3
	VAT, litres =0,370 x D -4,85

Conversion from adipose tissue volume to adipose tissue mass

Both genders:	AT, kg =AT, L x 0,923

Calculation of subcutaneous adipose tissue mass and lean body mass

Both genders:	LBM, kg =W, kg -Total AT, kg
	SAT, kg =Total AT, kg –VAT, kg

The errors of LBM, VAT and SAT resulting from these equations are in the order of 7 to 22%(36, 264) as compared to volume determinations by a multiscan CT technique (6, 31, 36).

3.8 Statistics

Statistical analysis were performed with Minitab Statistical Software 9.1 (Minitab Inc, State College, PA, US), Statistica for the Macintosh 4.1 (Statsoft Inc, Tulsa, OK, US), SAS Software 6.08 (SAS Institute Inc, Cary, NC, US) and Stata Statistical Software 6.0 (StataCorp, College Station, TX, US).

The Shapiro-Wilk test was used to evaluate whether variables were normally distributed. Non-normally distributed variables were log-transformed before analysis. Paired t-tests were used for within group comparisons. For comparisons of data between groups chi-square tests, two-sample t-tests and analysis of variance followed by Tukey's test were used. For comparison of changes in proportions between two groups a two-sample McNemar test(266) was used.

Pearson product moment correlation coefficients were used to evaluate univariate relations between variables. For relationships between several variables, multiple linear regression was used. As the two groups were matched on a group and not on an individual level unconditional logistic regression models were used for the comparisons of incidences between groups. Adjusted means were obtained according to the general linear model.

MAIN RESULTS

4.1 Paper I

Body compartments were closely related to risk factors in our severely obese subjects. By using the CT-calibrated anthropometric equations, a body composition – risk factor pattern was identified, within which VAT and SAT *masses* were positively related to risk factors while LBM showed negative relationships. In addition, a SAT *distribution* – risk factor pattern was defined. Here neck and thigh circumferences were used as indices of the SAT distribution. SAT in the upper part of the body was positively related to cardiovascular risk factors, while the reverse was true for a lower body SAT distribution (fig. 4.1). This was true also when taking the estimated body compartments into account. Although age and sex were strongly related to risk factors, these associations were markedly reduced when including body compartments and the SAT distribution into the model.

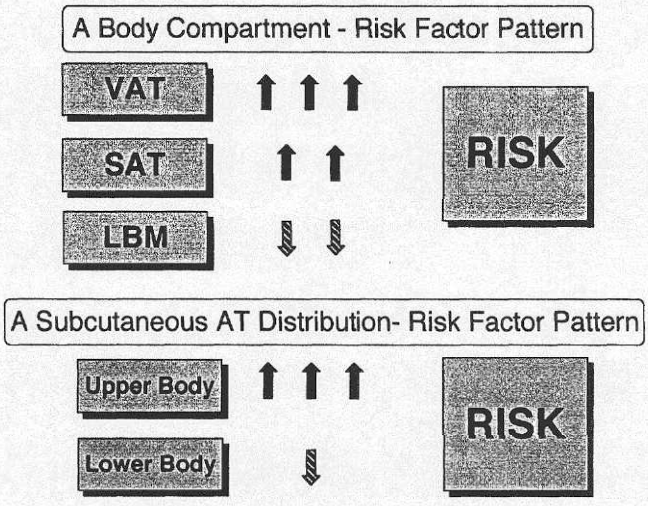

Figure 4.1. Two risk factor patterns in the severely obese.

4.2 Paper II

For the analysis of paper II, 401 controls and 441 surgically treated patients followed for 2 years were pooled in order to create a range of weight changes as wide as possible.

Change in body weight was related to change in body composition in the obese. VAT expressed in percent of total AT changed 6 times more in men than in women, for a given change in BMI.

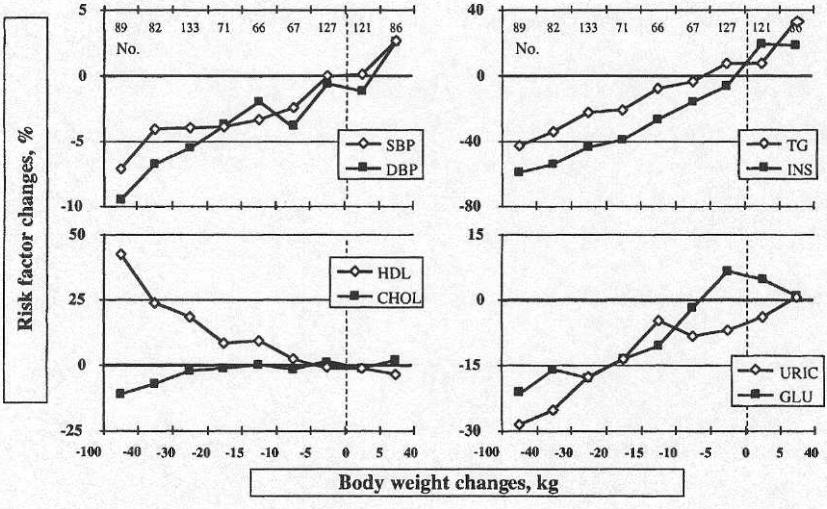

Figure 4.2. Adjusted risk factor changes (%) in relation to bodyweight changes (kg) over two years in 842 men and women with obesity. Adjustments are made for initial risk factor value, initial body weight, sex, age and height.

When examining univariate correlations between changes in risk factors and changes in anthropometric measurements; waist, BMI and body weight gave the highest explained variances in men. The same three variables gave the highest explained variances in women, but in reversed order. Several of the cross-sectional findings between risk

factors, body compartments and SAT distribution found in paper I (fig. 4.1) were confirmed longitudinally in paper II.

Weight decreases of at least 5 to 10 kg over two years were required in order to see any clinically important changes in most cardiovascular risk factors (fig. 4.2). An exception, was total cholesterol that required weight losses in the order of 30 to 40 kg in order to achieve persistent improvements after two years.

4.3 Paper III

Hardly any weight change was observed (-0.5±8.9 kg) in 712 conventionally treated controls followed for 2 years. Among 767 surgically treated patients the average weight loss was 28±15 kg.

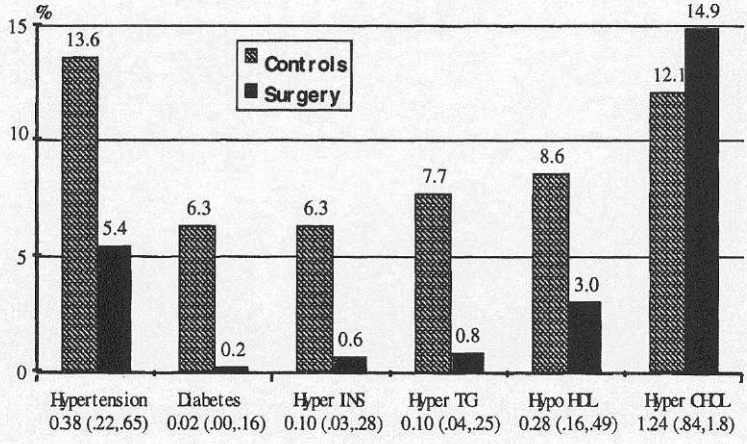

Figure 4.3. Two-year unadjusted incidence of indicated conditions (bars). Below bars odds ratios (95% CI) adjusted for baseline values of age, sex, weight, smoking and matching values of perceived health. P<0.001 except for hypercholesterolemia (NS).

All risk factors were significantly more reduced in the surgically treated group as compared to controls. Furthermore, the 2-year incidence of hypertension, diabetes, hyperinsulinemia, hypertriglyceridemia, hypo HDL-cholesterolemia was much lower in

the surgically treated group. The diabetes incidence was reduced 30-fold, while the other risk factor incidences were reduced between 2.6 and 10 times (fig. 4.3). There was no difference in the development of hypercholesterolemia.

Weight change over the first year was used to divide all individuals in three subgroups (see table 2 in paper III). When compared with subjects increasing their body weight on average by 4% (0-26% weight increase) over the first year, a weight decrease of 9% (19.9-0.1% weight loss) was sufficient to decrease the 2-year incidence of diabetes, hyperinsulinemia, hypertriglyceridemia and hypo-HDL-cholesterolemia. In order to detect a significant effect on the incidence of hypertension after 2 years an average weight reduction of 30% (56 to 20% weight loss) was required after one year. Concerning the incidence of hypercholesterolemia, no significant differences were obtained between the three categories of weight change.

4.4 Paper IV

After a follow-up of eight years 251 surgically treated patients were still 16±12 % below their inclusion body weight. The 232 conventionally treated patients followed for the same period had increased their body weight 1±11 % (fig. 4.4).

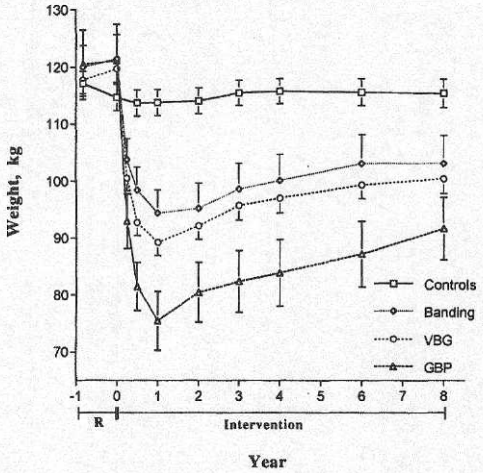

Figure 4.4. Weight change (95%CI) in 232 obese controls and 251 surgically treated obese patients from matching until end of year 8.

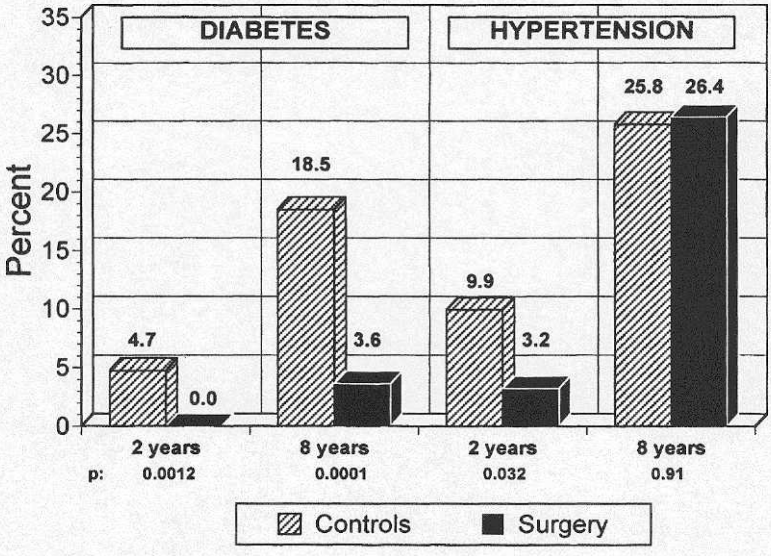

Figure 4.5. Two and eight-year unadjusted incidences of diabetes and hypertension among controls and surgically treated patients.

In agreement with paper III, the 2-year incidence, of diabetes as well as hypertension was reduced in the surgically treated group as compared to controls (fig. 4.5). However, the initially reduced blood pressures in the surgically treated group started a relapse six months after inclusion leaving no significant difference in SBP between the groups after eight years (fig. 4.6). In the end of the study period, DBP was even higher in the surgically treated group as compared to the control group. This was also true after adjustments for sex, age, inclusion weight, inclusion blood pressure, blood pressure medication, smoking, alcohol intake, energy intake and physical activity during work and leisure (fig. 4.6).

Consequently, the eight-year incidence of hypertension did not differ between controls and surgical intervention patients, whereas the 8-year incidence of diabetes was 5 times as high among controls as in the intervention group (fig. 4.5).

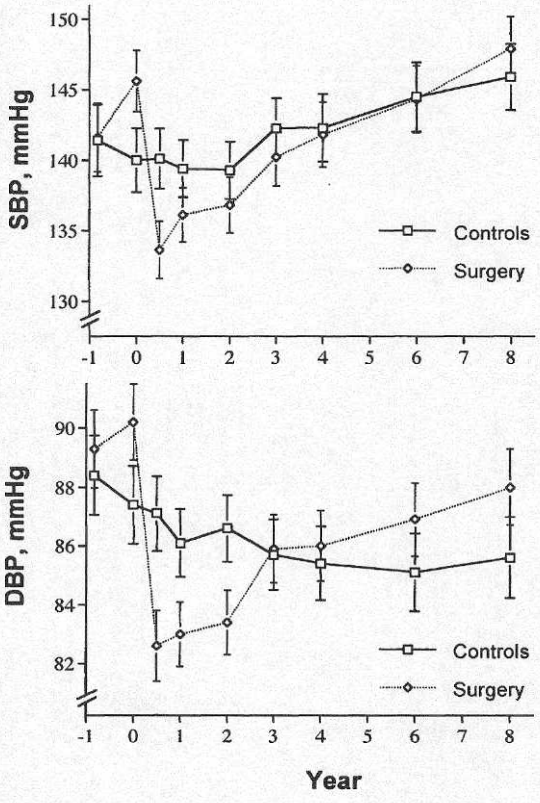

Figure 4.6. Development of adjusted SBP and DBP (95% CI) over 8 years in 232 obese controls and 251 surgically treated obese patients.

4.5 Paper V

The unexpected long-term development in blood pressure (fig. 4.6) was further investigated in 1031 controls and 1157 operated patients followed for an average of 5.5 years (range: 3 to 10 years).

By dividing these patients into five cohorts based on length of follow-up, it was possible to separate the effects of ageing from that of weight regain per unit of time. Among surgically treated patients, it was shown that the effect on final blood pressure exerted

by one year of ageing was 2.5 to 4 times as large as the effect of one regained kilo during the last year of observation. Furthermore, one regained kilo during the last year of observation had about twice as large an impact on final blood pressure as an initial one kilo difference in body weight ,or as one kilo lost during the first year's rapid weight decrease.

Further analyses of the development of different pressures in the specific treatment groups were made. Despite relapsing blood pressures in the surgical intervention group, bariatric surgery still had a modulating effect on the rapid increase in PP seen in the obese (table 3). There were, however, large differences in blood pressure and PP response to different surgical techniques.

Table 3. Adjusted delta pressures (95% CI) by treatment assignment.

Treatment groups	Δ PP	Δ SBP	Δ DBP
Controls, n:1026	4.7 (3.9, 5.6)	1.6 (0.6, 2.7)	-3.2 (-3.8, -2.5)
VBG, n:829	3.7 (2.8, 4.6)	2.7 (1.6, 3.9)	-1.0 (-1.7, -0.3)†
GB, n:255	1.4 (-0.2, 2.9)†	-0.3 (-2.4, 1.8)	-1.7 (-2.9, -0.5)*
GBP, n:68	-1.5 (-4.6, 1.6)†	-8.3 (-12.3, -4.4)†	-6.7 (-9.0, -4.3)*
Surgery, n:1152	2.9 (2.1, 3.7)*	1.4 (0.4, 2.4)	-1.5 (-2.1, -0.9)†

*Values are mean changes from inclusion to last observation (95% CI). Adjustments are made for sex, follow-up time, inclusion: age, weight, height and BP, and to values at the last observation of: smoking (yes/no), alcohol intake (g/day), BP-medication (yes/no). Difference to controls: * $p<0.05$, † $p<0.001$. VBG, vertical banded gastroplasty; GB, gastric banding; GBP, gastric bypass.*

DISCUSSION

5.1 Body composition

Evolution of estimates

The terms *upper body* and *abdominal obesity* are often used in a poorly defined manner. Different authors are using these terms for increased VAT, increased abdominal SAT, increased trunk SAT or increased SAT in the scapular and /or arm regions or for different combinations of these increases. Upper body obesity or abdominal obesity has also been defined as an increased WHR, but this condition has been differently interpreted over the years. Originally, WHR was used in order to relate the metabolicly active abdominal SAT to adverse cardiovascular risk profiles(24, 25, 267). As interest turned towards VAT(40, 268) the assumed implication of an increased WHR turn from abdominal SAT with an intermediate metabolic turnover rate to the highly active intra-abdominal fat depot.

In order to evaluate the effects of a rather undefined *regional adiposity* apart from the effects of total adiposity, WHR have been adjusted for BMI(34). This kind of epidemiological studies(34, 44) are important to relate cardiovascular risk to measurable anthropometric variables. However, they do not bestow any biological understanding of which AT depots that are important in generating cardiovascular risk factors.

In the model presented in paper I, we have combined the notion of upper and lower body SAT distribution of Vague with the more recent notion of VAT. In contrast to earlier epidemiological approaches, the new techniques permit estimations of the quantities of SAT, VAT and LBM in kilograms. Papers I and II have shown that all three body compartments and the SAT distribution independently contribute to the metabolic risk factor profile, both cross-sectionally and longitudinally. It must be emphasised that weight, height and sagittal diameter, from which the three estimates of body compartments are derived, give the same explained variances as LBM, SAT and VAT when used in multivariate regressions with any risk factor as dependent variable. However, it seems useful to translate anthropometric measurements into body compartments, since this helps to interpret the biological relationships between body composition and risk factors. The translation is based on mathematical relationships

between anthropometric variables and CT-determined body compartments established in other and independent studies.

Importance and pathogenetic links

In epidemiological studies, weight loss is usually associated with increased mortality rate(213). In a recent study on weight change and mortality(222), Allison et al. used skinfolds as a rough assessment of body fat. While weight loss increased mortality rate, fat loss decreased mortality. Of course, Allison's results or those of papers I and II would have had a much higher resolution if undertaken with CT, MRI, DEXA, neutron activation or other advanced body composition techniques. However such techniques are expensive and time consuming and therefore not possible to use in a number of settings. Thus, *interpretable anthropometry* may have an important function to fulfil and papers I and II have made use of such a technique.

Several studies have demonstrated that risk factors are closer related to VAT than SAT in study groups consisting of lean to *moderately* obese individuals(269). Paper I and II have demonstrated similar relationships between body composition and risk factors in *severely* obese patients. In fact, papers I and II are the first to demonstrate the importance of fat patterning cross-sectionally and longitudinally in the BMI range 28-68 kg/m^2 for a large number of subjects. Most risk factors were related to AT distribution even in men (36.9-63.8 kg/m^2) and women (40.1-68 kg/m^2) above median BMI values.

The associations between AT distribution and metabolic aberrations may be explained by common background factors causing metabolic aberrations as well as a given AT distribution(50), but also by a pathogenic role *per se* of VAT and of SAT located in the upper parts of the body. Although the total FFA release from VAT is less than that from SAT(99, 100), the first passage effect of FFA originating from the portal system may give VAT a disproportional high influence on hepatic insulin clearance(40). Furthermore, the FFA release per kg is larger from SAT in the upper than in the lower part of the body as measured in vivo(100). This is in analogy with the finding, that risk factors are inversely related to neck and thigh circumferences, when the masses of SAT and VAT are taken into account. Taken together, this indicates that the SAT distribution also has an impact on insulin clearance and peripheral insulin resistance via the FFA mechanism. This suggestion helps to explain why subcutaneous skinfolds from the upper part of the body are related to the incidence of coronary heart disease(130) as well

as all-cause mortality(222), in spite of the fact that these skinfolds apparently must be poorly related to the VAT mass.

Validity of the used technique

Our observations assume that it is possible to estimate LBM, SAT and VAT from weight, height and the sagittal trunk diameter and also that the neck and thigh circumferences reflect upper and lower SAT distribution, respectively.

With the CT based multicompartment technique based on 22 or 28 scans VAT, SAT and LBM can be determined with precision errors being smaller than 1%(6, 31, 35, 265). The accuracy of the CT technique has been examined in various ways. In the 13-compartment model based on 28 scans, each compartment volume was multiplied with its density to obtain estimates of compartment weights. The sum of these weights constituted a CT estimate of body weight (BW_{CT}). The difference between BW_{CT} and actually measured body weight (BW) was 0.024 ± 0.65 kg and the error calculated on the squared differences was 0.6 kg or 0.85% of body weight(31). Furthermore, the slope was close to 1.0 and the intercept close to zero when BW_{CT} was regressed by BW and a Bland-Altmann analysis did not support that BW_{CT} was biased by BW(31). This type of validation does not exclude the possibility that hidden errors in the determination of compartment weights are balancing out each other. The likelihood for hidden errors has been considerably reduced since changes in body weight agree closely with net changes of body compartments both when fat and lean tissues are changing concordantly and disconcordantly(270-272). Thus, the reference method used for development of the anthropometric equations fulfils high requirements.

The CT calibrated, sex specific, anthropometric equations in our model were originally based on a group of 17 men and 10 women with a wide range of body weights (46-145 kg). The equations were cross-validated in a similar group of 7 men and 9 women(264). Linear conditions were observed up to 145 kg and only 3.5% of the patients examined in papers I and II were above 145 kg. With available CT scanners, this limitation is inevitable since subjects heavier than 145 kg can not usually be examined. The error, calculated as the standard error of a single determination(273), is less than 21% for VAT and less than 11% for total AT(264) when results obtained by the anthropometric equations are compared with those of the multiscan CT-technique. Later, the relationship between sagittal diameter and VAT volumes was validated in another group of 13 males(265) resulting in smaller errors than in the original paper(264). The

equations have also been shown to be valid for healthy males of Indian origin(274). The sagittal diameter overestimated VAT in men and women with acromegaly, a condition characterised by a dramatic increase of LBM and marked reductions of VAT and SAT(36). One year after treatment of the acromegalic patients, the anthropometric equations were valid again(36).

In our studies, the sagittal diameter has always been superior to the waist circumference in predicting VAT(36). This has not been the case in all study groups examined by others(275, 276). However, studies finding the waist circumference superior to the sagittal diameter in predicting VAT have used area determinations of single CT or MRI scans rather than volume determinations from multiple scans. Results from single scans can be very misleading, since the distribution of VAT has a large inter-individual variation(36). In fact, the VAT area of one CT scan is only marginally better than the sagittal diameter in predicting the VAT volume determined with multiscan technique(36). Therefore, the VAT area of single scans is a sub-optimal standard when developing anthropometric equations.

With the multiscan CT-technique it has also been confirmed that the anthropometric equations for males estimate *changes* in VAT and total AT correctly(277). Corresponding evaluations for females have not been published by the Gothenburg group. Other investigators have confirmed the advantages of sagittal diameter in detecting changes in VAT in men but not in women(275) and that WHR(278) and waist circumference(279) have a poor ability of detecting changes in VAT.

Furthermore, the body composition model in paper I and II assumes that neck and thigh circumferences reflect the SAT distribution. In multivariate regressions, these circumferences were much closer related to the estimated SAT mass than to the estimated LBM. These statistical findings indicate, that muscles and skeleton have a limited influence on the neck and thigh circumferences as compared to SAT, in an obese population. This was an expected finding since AT can vary in volume several fold more than any other tissue. Thus, when the SAT mass is taken into account statistically (as in all regressions of risk factors in paper I and II) it is likely that the neck and thigh circumferences reflect the SAT distribution. Even if SAT (obtained from weight, height and the sagittal diameter) is adjusted for, it can not be excluded that the neck circumference also reflects general obesity to some extent. However, this can

hardly be the case for thigh circumference, since thigh is negatively related to risk factors when SAT and neck are taken into account.

In simple and multivariate regressions, the neck and thigh circumferences were also related to VAT. These relations must be indirect since no VAT is present in the neck and thigh regions. Interestingly, treatment studies of patients with Cushing's disease(270) and with growth hormone deficiency(271) indicate that the volumes of neck AT and VAT, determined with multiscan CT-technique, are changing in parallel. This may be due to regulatory mechanisms in common for the two tissues.

Risk factors, anthropometry, gender and age

Two gender differences of potential interest were observed in paper I. Firstly, thigh circumference and VAT mass were positively related in men but negatively related in women when the SAT mass was kept constant. Thus, SAT mass in the lower part of the body and the VAT mass seem to be inversely regulated in women. Secondly, triglycerides tended to be or were negatively related to age in obese males. This relation was observed when body composition was kept constant. In obese females, however, triglycerides were positively related to age, a finding that was explained by body composition. These findings seem to be in accordance with the idea that triglycerides is a more important risk factor in women than in men(30).

It has also been demonstrated in randomly selected men and women that gender loses its explanatory power with respect to the incidence of myocardial infarction when the WHR is taken into account(30). This observation suggests that incidence differences between sexes may partly be explained by differences in AT distribution. The findings in paper I extend the previous observations(30) and demonstrate that body compartments estimated by CT calibrated anthropometry are even more efficient than the WHR in eliminating the explanatory power of sex when analysing risk factors in study groups containing both genders.

Within each gender, the three estimated body compartments plus neck and thigh reduced the explanatory power of age for some but not for all risk factors while the explanatory power of age seemed to be less markedly reduced by BMI plus WHR (paper I). Although not totally consistent, these findings are in line with the fact that in both genders age was positively related to the VAT mass and negatively to the thigh

circumference(paper I). CT based studies have confirmed an increased amount of VAT with age(280, 281).

The findings discussed above indicate that our anthropometric model plus neck and thigh girths reflect the effects of age and gender on body composition more efficiently than traditional anthropometric variables. This is further supported by the fact that our model also explained the variance of all examined risk factors more efficiently than BMI, waist and hip (paper I).

Weight loss and changes in anthropometry

In paper II, strong positive correlations between changes in BMI and changes in both waist circumference and sagittal diameter were observed. The changes for a given change in BMI seemed to be larger in men than in women. In both genders, changes in WHR displayed weaker associations with weight change, reflecting an independent variability in the hip-circumference in response to weight change, particularly in women. Neither sagittal diameter, waist or WHR as such reflects the true change in relative amount of VAT in men or women. This is related to the facts that women have more SAT and that a given change in sagittal diameter corresponds to twice as large a change of VAT mass in men as in women. When taking these circumstances into account it was demonstrated that the relative amount of VAT (i.e. VAT mass in percent of total AT mass) was changing 6 times more in men than in women for a given change in BMI.

After an 18% weight reduction both men and women seemed to have a larger relative decrease in VAT mass (41 and 31%, respectively) than in SAT mass (28 and 26%, respectively). A larger relative decrease in VAT after weight loss has been confirmed by others in smaller studies where VAT has been measured by CT or MRI(224, 278).

There were also gender differences with significantly larger relative reductions of VAT mass and LBM in men as compared to women after the same degree of weight loss (Paper II). Most(224) but not all(282) CT studies confirm a larger proportional loss of VAT in men than in women. This difference was also confirmed in a recent meta-analysis by Smith and Zachwieja(283). They reviewed 23 studies that had assessed the effects of weight change on body composition as measured by direct methods. They found that individuals with a larger VAT/abdominal SAT ratio tended to lose more VAT than persons with less VAT. Considerable overlap was seen between men and

women. This might suggest that the relative amount of VAT loss is not due to gender per se, but is rather related to the initial AT distribution.

5.2 Risk changes in relation to weight changes

Changes in risk factors and anthropometry

Univariate correlations between changes in single anthropometric variables and changes in cardiovascular risk factor were strongest for waist , BMI and body weight. In males, Δ waist and Δ BMI were closest related to risk factor changes, while in women, Δ body weight and Δ BMI seemed to be closer related to risk factor changes than Δ waist. Change in sagittal diameter was less related to risk factor changes in both men and women.

Multivariate analyses with adjustments for Δ BMI and baseline conditions clarified these univariate results further. Δ BMI was the strongest predictor, followed by Δ VAT or Δ sagittal diameter. In contrast, Δ waist and Δ WHR performed poorly when adjusted for change in BMI. As compared to Δ sagittal diameter, Δ VAT seemed to be even closer related to changes in risk factors. This further illustrates the potential of using body compartments estimated by sex specific equations rather than raw anthropometric measurements, when analysing study groups containing both men and women.

In the light of the poor longitudinal performance of waist, when adjusted for BMI, it may seem strange that population specific risk limits of waist circumference are currently being put forward(4) (see 1.3). However, the above mentioned results illustrate the dual relationships of waist. While change in waist circumference alone is closely correlated to changes in risk factors, it loses predictive power when adjusted for change in BMI. This may be related to the fact that waist is closer associated with BMI and SAT than with VAT(36), and to the fact that changes in several risk factors may be even closer related to changes in SAT than to changes in VAT as demonstrated in paper II. Only changes in insulin and TG were closer related to changes in VAT as compared to SAT.

Therefore, in spite of the fact that sagittal diameter is the optimal predictor of VAT volume(36), waist as a single predictor may be equally good or better as a risk factor indicator, both under cross-sectional and longitudinal conditions.

Risk factors and weight loss

Our results generally showed proportionally increasing cardiovascular risk factor benefits with increasing weight reduction (paper II and III). It is interesting to note that the small amounts of weight loss (5 to 10 kg) generally considered to reduce risk factors in moderately obese subjects(211, 212, 226) also decreased most risk factors after two years in the severely obese subjects of paper II. This may be due to the relatively larger loss of VAT as compared to SAT for a given weight reduction, as discussed above.

However, not all risk factors responded to small weight losses. Total cholesterol required weight losses of more than 30 kg before any noticeable improvement could be observed after two years (Paper II). This is reflected in paper III, where no difference in the 2-year incidence of hypercholesterolemia was observed in individuals who had lost 30% after one year as compared to those who had gained 4%. For diabetes, hyperinsulinemia, hypertriglyceridemia and hypo-HDL-cholesterolemia a decrease of 9% after one year gave significant reductions in the two-year incidences. Concerning hypertension, a significantly reduced two-year incidence was observed after a weight loss of 30% (Paper III).

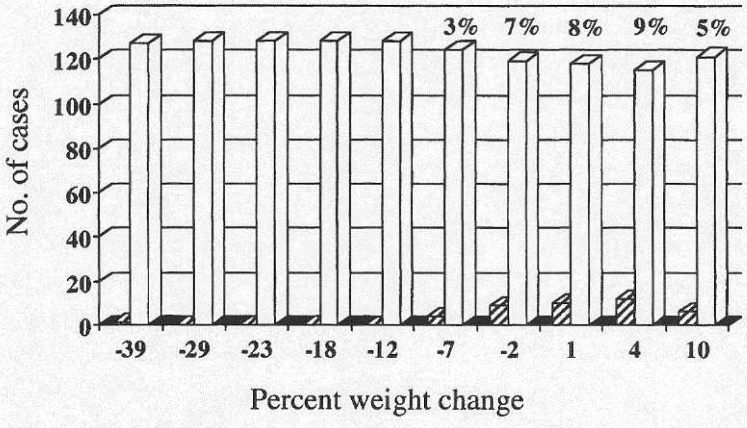

Figure 5.1. Two-year incidence of diabetes by decentiles of percent weight change in the pooled control and surgically treated g roups. Data based on 1281 individuals not having diabetes at baseline. Striped bars indicate new cases of diabetes. Numbers at the top of bars indicate the percentage with diabetes after two years in that decentile. Not previously published.

Unfortunately, the statistical power did not permit divisions in more than three weight changing classes, resulting in a small resolution. Division of the 2-year weight loss by decentiles gives a more detailed, visual impression of the critical cut-off in weight loss, as illustrated for the incidence of diabetes in figure 5.1. Due to small numbers in each weight loss decentile, the incidence figures are somewhat unstable between adjacent groups. However, figure 5.1 suggests that no new cases of diabetes were seen if the weight loss was larger than 7% over two years.

At eight years, a 16% weight loss had no effect on the incidence of hypertension in spite of a marked effect on the diabetes incidence. In a recent investigation conducted by Wadden(225), total and LDL cholesterol started to relapse after 24 weeks while TG even decreased further. Similar results were obtained in an orlistate trial(226).

Taken together, these observations illustrate that degree of weight loss, observation time as well as risk factor under consideration determine whether a risk factor relapse will be observed or not.

Weight loss and long-term effects on blood pressure

In our eight-year follow-up (paper IV), we found reduced two-year incidences for hypertension and diabetes in surgically treated patients as compared to controls. However, at 8 years there was no difference in the incidence of hypertension, although the incidence of diabetes was five times higher in controls than in surgically treated patients.

These long-term results are not in agreement with earlier controlled studies with a shorter follow-up indicating effect of weight loss on blood pressure in hypertensive as well as normotensive subjects(209). Where other investigators have concluded that even small (2-3 kg) net weight losses might be beneficial for the control of hypertension(284), paper IV shows that over a long period not even a maintained 16% weight loss is sufficient to achieve a reduction of the 8-year incidence in the severely obese. These new findings are also in conflict with previous, uncontrolled surgical obesity studies with shorter follow-up indicating a favourable effect on hypertension(285, 286). A regain of blood pressure after weight loss has been shown also in other studies. However, the follow-up periods have usually been too short to allow a complete relapse(226, 285, 287, 288).

Blood pressure reductions after weight loss have been associated with improvements of insulin resistance and suppression of sympathetic nervous activity(289). Many studies have proposed insulin as a sympathetic activator(290) and as a link between diabetes and hypertension(140). Given the divergent effects of weight reduction on diabetes and hypertension, insulin does not seem to be the only mediator of hypertension or sympathetic nervous system hyperactivity seen in the obese. This observation is supported by a recent cross-sectional observation, that central obesity as measured with the sagittal diameter is independently related to blood pressure, and that insulin may account for only a part of this association(291).

Blood pressure relapse

Paper V visualises the independent effects of time (ageing) and weight regain on blood pressure. This was possible by using cohorts of patients with different length of follow-up.

The final blood pressure in the operated population was not equally related to an earlier lost and a later regained amount of weight. In fact, a given weight regain in the later parts of the study had almost twice as large an impact on final blood pressure as a corresponding difference in inclusion weight or the same degree of weight loss in the beginning of the study. These results are in agreement with an observational study showing that ongoing weight increase is of greater importance for current blood pressure than baseline body weight(292). Furthermore, Dornfeld has shown that blood pressure levels are higher during weight increase than during weight decrease when passing the same absolute weight(288). This may be related to a higher SNS activity during weight increase than during weight loss(293).

Paper V also shows that the effect on blood pressure of one elapsed year was 2.5 to 4 times larger than the effect of one regained kilo. This is an important point, which previous blood pressure studies have not taken into account. While the effect of time on SBP was the same among controls as in the surgically treated group, no significant association between follow-up time and DBP was found in the control group. This was related to a slope closer to zero for DBP vs. time in the obese controls than for other pressure changes observed in this study.

Pulse pressure development and risk

Despite several reports about the hazards of isolated systolic hypertension in middle-aged and older persons(294, 295), increased diastolic blood pressure was regarded as the main threat for a long time. SBP elevation out of proportion to DBP is common. If using the latest JNC-VI staging of hypertension on a middle-aged population, potentially eligible for drug therapy, SBP alone correctly classifies JNC-VI stage in 91%, whereas DBP alone correctly classifies only 22% of the individuals(296). Whereas SBP increases almost linearly with age until a high age, DBP reaches a peak in the late 50s and then declines(295, 297).

Results from the Seven countries study show a clear association between increased DBP and mortality from CHD in men aged 40 to 59 years(298). The same observation was true in men and women aged 50 to 79 years in the Framingham study(299). However, in the Framingham study, when adjusting for SBP the relationship between CHD and DBP became significantly negative(299). Lee and co-workers showed no relationship at all between DBP and cardiovascular death in men aged 60-85. Nevertheless, when adjusting for SBP the association between DBP and mortality became negative(300).

Ageing and hypertension are both associated with reductions in arterial compliance, leading to an increased arterial pulse wave amplitude and velocity, with an early return of reflected waves to the aorta(301). These aberrations are ensued by increased SBP, decreased DBP and, evidently, an increased pulse pressure. Pulse pressure has appeared as an independent predictor of coronary heart disease(299), carotid stenosis(302), cardiovascular mortality(300, 303) as well as stroke and all-cause mortality(304).

The increase in pulse pressure is seen as a consequence of an increasing arterial stiffness(305) and has been associated with an increased intima-media thickness(306). In an earlier SOS-report it was shown that the progression rate of the intima-media thickness in the carotid bulb of obese weight stable subjects is three times faster than in age-matched lean controls(307). It was also shown that the surgically induced weight reduction normalised this progression rate(307). These observations are in line with our finding that a maintained large weight reduction slows the rapid increase in pulse pressure seen in weight stable severely obese subjects (paper V).

There were discrepancies concerning the effect on pulse pressure between the different surgical techniques. VBG had a less pronounced effect on pulse pressure as compared to

GB and GBP. The reasons for this have not been clarified as GB and VBG resulted in similar weight losses. If this is a chance finding or an observation related to different effects of GB and VBG on gastrointestinal signalling is an open question. The most favourable response in blood pressure and pulse pressure was seen in GBP patients. GBP is associated with increased releases of GLP-1 after meals, and GLP-1 has weight reducing as well as anti-diabetic properties(247).

CONCLUSIONS

A previously developed procedure for *interpretable anthropometry* giving VAT, SAT and LBM from weight, height and sagittal diameter was used in papers I and II. Neck and thigh circumferences were added to this procedure as indices of SAT distribution. One body compartment - risk factor pattern and one SAT distribution - risk factor pattern were demonstrated in obese subjects. Within the first pattern, cardiovascular risk factors are positively related to the SAT and VAT masses but negatively related to LBM. Within the second pattern risks are positively related to an upper body but negatively related to a lower body SAT distribution.

Changes in cardiovascular risk factors were independently related to changes in SAT and VAT. The relative change in VAT was larger in men than in women. Changes in risk factors were reflected to a similar degree by unadjusted changes in waist circumference, BMI and body weight. Weight losses of 10 kg over two years resulted in improvements in most risk factors.

The two-year incidence of hypertension, diabetes, hyperinsulinemia, hypertriglyceridemia and hypo HDL-cholesterolemia was markedly reduced in the surgically treated group as compared to weight stable controls. The diabetes incidence was reduced 30-fold, while the other risk factor incidences were reduced between 2.6 and 10 times. There was no difference in the development of hypercholesterolemia between the two groups.

A differentiated risk factor response was identified concerning the eight-year incidences of diabetes and hypertension. Whereas diabetes is favourably influenced by an intentionally reduced body weight, the effect on hypertension seems to be of a transitory nature. No difference in the eight–year incidence was detected despite a maintained 16% weight reduction in the surgically treated group.

The relapse in blood pressure seen after surgically induced large weight losses in still obese subjects is more related to ageing and recent small weight increases than to inclusion weight or initial weight losses.

Weight-reducing gastric surgery slows the rise in pulse pressure seen in weight stable obese controls. This may indicate that weight loss could reduce the elevated progression rate of the atherosclerotic process observed in obese subjects.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all who have contributed to this thesis. Special thanks to:

Lars Sjöström, my tutor, father and above all friend, for many great moments and memorable excursions in science and the world.

Markku Peltonen, co-author, for cheerfully solving all sorts of statistical and computer related problems and for sharing many late meals at SOS with me and his master's voice during a long autumn.

My co-authors, *Camilla Håkangård, Lauren Lissner* and *Hans Wedel* for enjoyable collaboration and skilful contributions to this work.

My friends and research colleagues, *Jarl Torgersson, Kristjan Karason, Kaj Stenlöf, Tom William-Olsson, Lars Lönn* and *Peter Jacobsson* for many good laughs. *Kristina Narbro* and *Anna Karin Lindroos* for many good laughs and for invaluable practical help with the SOS databases.

Lisbeth Eriksson and the staff at the SOS secretariat *Gerd Bergmark, Mona Falkman, Rose-Marie Johansson, Eva Olausson, Margareta Rystedt* and *Ingrid Vinsa* for keeping every thing going and for great Friday pastries.

Helén Lantz and every one at U-lab and in the cellar, for a cheerful atmosphere.

The Department of Anaesthesiology and Intensive Care, for letting me escape from the calls.

The members of the steering, laboratory and safety monitoring committees of SOS as well as the staff at 25 surgical departments and 480 primary health care centers in Sweden, for excellent help and co-operation.

Finally Bistro Amica, for the pancakes.

REFERENCES

1. Brown PJ, Konner M. An anthropological perspective on obesity. Ann N Y Acad Sci 1987;499:29-46.
2. Trowell HC, Burkitt DP. Western diseases: their emergence and prevention. Cambridge: Harvard University Press; 1981.
3. Hill JO, Peters JC. Environmental contributions to the obesity epidemic. Science 1998;280:1371-4.
4. WHO. Obesity: Preventing and Managing the Global Epidemic - Report of a WHO Consultatin on Obesity. Geneva: World Health Organization; 1998.
5. Quetelet LAJ. Anthropometric où misure des differentes facultes de l'homme. Brussels: C Marquardt; 1871.
6. Sjöström L, Kvist H, Cederblad A, Tylén U. Determination of total adipose tissue and body fat in women by computed tomography, 40K, and tritium. Am J Physiol 1986;250:736-45.
7. Kvist H, Chowdhury B, Sjöström L, Tylén U, Cederblad A. Adipose tissue volume determination in males by computed tomography and 40K. Int J Obes 1988;12:249-66.
8. Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr 1991;65:105-14.
9. Van Itallie TB. Health implications of overweight and obesity in the United States. Ann Intern Med 1985;103:983-8.
10. Waaler HT. Height, weight and mortality. The Norwegian experience. Acta Med Scand 1984;679 (Suppl):1-56.
11. Bray GA. Complications of obesity. Ann Intern Med 1985;103:1052-62.
12. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097-105.
13. James WP, Ralph A. New understanding in obesity research. Proc Nutr Soc 1999;58:385-93.
14. Reilly JJ, Dorosty AR. Epidemic of obesity in UK children. Lancet 1999;354:1874-5.
15. Rasmussen F, Johansson M, Hansen HO. Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995. Acta Paediatr 1999;88:431-7.
16. Seidell JC. Obesity in Europe. Obes Res 1995;3(Suppl 2):89-93.
17. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J Obes Relat Metab Disord 1998;22:39-47.
18. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-9.

19. Actuaries So. Build and blood pressure study1959. New York: Peter F. Mallon Inc; 1959.
20. Lee IM, Manson JE, Hennekens CH, Paffenbarger RS, Jr. Body weight and mortality. A 27-year follow-up of middle-aged men. JAMA 1993;270:2823-8.
21. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. J Chronic Dis 1979;32:563-76.
22. Vague J. Sexual differentiation. A determinant factor of the forms of obesity. (1947, classical article). Obes Res 1996;4:201-3.
23. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. (1956, classical article). Obes Res 1996;4:204-12.
24. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982;54:254-60.
25. Krotkiewski M, Björntorp P, Sjöström L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 1983;72:1150-62.
26. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J 1984;288:1401-4.
27. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J 1984;289:1257-61.
28. Lundgren H, Bengtsson C, Blohmé G, Lapidus L, Sjöström L. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. Int J Obes 1989;13:413-23.
29. Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985;34:1055-8.
30. Larsson B, Bengtsson C, Björntorp P, Lapidus L, Sjöström L, Svardsudd K, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women, Goteborg, Sweden. Am J Epidemiol 1992;135:266-73.
31. Chowdhury B, Sjöström L, Alpsten M, Kostanty J, Kvist H, Löfgren R. A multicompartment body composition technique based on computerized tomography. Int J Obes Relat Metab Disord 1994;18:219-34.

32. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460-8.

33. Richelsen B, Pedersen SB. Associations between different anthropometric measurements of fatness and metabolic risk parameters in non-obese, healthy, middle-aged men. Int J Obes Relat Metab Disord 1995;19:169-74.

34. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. JAMA 1998;280:1843-8.

35. Sjöström L. A multicompartment technique based on computerized tomography. In: Angel A, Anderson H, Bouchard C, Lau D, Leiter L, Mendelson R, editors. Progress in Obesity Research: 7. London: John Libbey & Company Ltd; 1996. p. 321-4.

36. Sjöström L, Lönn L, Chowdhury B, Grangård U, Lissner L, Sjöström D, et al. The sagittal diameter is a valid marker of the visceral adipose tissue volume. In: Angel A, Anderson H, Bouchard C, Lau D, Leiter L, Mendelson R, editors. Progress in Obesity Research: 7. London: John Libbey & Company Ltd; 1996. p. 309-19.

37. WHO Expert Committee on Physical Status. The use and interpretation of anthropometry: Report of a WHO Expert Committee. Geneva: World Health Organisation; 1995.

38. Sugerman H, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. J Intern Med 1997;241:71-9.

39. Seidell JC, Andres R, Sorkin JD, Muller DC. The sagittal waist diameter and mortality in men: the Baltimore Longitudinal Study on Aging. Int J Obes Relat Metab Disord 1994;18:61-7.

40. Björntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 1990;10:493-6.

41. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ 1995;311:158-61.

42. Han TS, van Leer EM, Seidell JC, Lean ME. Waist circumference action levels in the identification of cardiovascular risk factors: prevalence study in a random sample. BMJ 1995;311:1401-5.

43. Han TS, van Leer EM, Seidell JC, Lean ME. Waist circumference as a screening tool for cardiovascular risk factors: evaluation of receiver operating characteristics (ROC). Obes Res 1996;4:533-47.

44. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life in people with large waist circumference. Lancet 1998;351:853-6.

45. Dowling HJ, Pi-Sunyer FX. Race-dependent health risks of upper body obesity. Diabetes 1993;42:537-43.

46. Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in hong kong chinese. Int J Obes Relat Metab Disord 1999;23:1136-42.
47. Molarius A, Seidell JC, Sans S, Tuomilehto J, Kuulasmaa K. Varying sensitivity of waist action levels to identify subjects with overweight or obesity in 19 populations of the WHO MONICA Project. J Clin Epidemiol 1999;52:1213-24.
48. Després JP. Lipoprotein metabolism in visceral obesity. Int J Obes 1991;15 Suppl 2:45-52.
49. Torgersson JS, Rydén A, Karlsson J, Palaszewski B, Sullivan M, Sjöström L. BMI is more important than mental distress for cardiovascular risk factors in obese men. (Submitted) .
50. Björntorp P, Rosmond R. Visceral obesity and diabetes. Drugs 1999;58(Suppl 1):13-8.
51. Sjöström L. The metabolic syndrome of human obesity. In: Bouchard C, Bray GA, editors. Regulation of body weight: biological and behavioral mechanisms. Chichester: John Wiley & Sons Ltd; 1996. p. 61-83.
52. Kraus-Friedmann N. Hormonal regulation of hepatic gluconeogenesis. Physiol Rev 1984;64:170-259.
53. Holmäng A, Björntorp P. The effects of cortisol on insulin sensitivity in muscle. Acta Physiol Scand 1992;144:425-31.
54. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose-fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785-9.
55. Björntorp P. Visceral obesity: A 'Civilization syndrome'. Obes Res 1993;2:206-22.
56. Mårin P, Darin N, Amemiya T, Andersson B, Jern S, Björntorp P. Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism 1992;41:882-6.
57. Pasquali R, Cantobelli S, Casimirri F, Capelli M, Bortoluzzi L, Flamia R, et al. The hypothalamic-pituitary-adrenal axis in obese women with different patterns of body fat distribution. J Clin Endocrinol Metab 1993;77:341-6.
58. Epel EE, Moyer AE, Martin CD, Macary S, Cummings N, Rodin J, et al. Stress-induced cortisol, mood, and fat distribution in men. Obes Res 1999;7:9-15.
59. Bray GA. Obesity, a disorder of nutrient partitioning: the MONA LISA hypothesis. J Nutr 1991;121:1146-62.
60. Bray GA, York DA. The MONA LISA hypothesis in the time of leptin. Recent Prog Horm Res 1998;53:95-117.
61. Landsberg L, Troisi R, Parker D, Young JB, Weiss ST. Obesity, blood pressure, and the sympathetic nervous system. Ann Epidemiol 1991;1:295-303.
62. Karason K, Mølgaard H, Wikstrand J, Sjöström L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999;83:1242-7.

63. Andersson B, Elam M, Wallin BG, Björntorp P, Andersson OK. Effect of energy-restricted diet on sympathetic muscle nerve activity in obese women. Hypertension 1991;18:783-9.

64. Vollenweider P, Randin D, Tappy L, Jequier E, Nicod P, Scherrer U. Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle in obese humans. J Clin Invest 1994;93:2365-71.

65. Attvall S, Eriksson BM, Fowelin J, von Schenck H, Lager I, Smith U. Early posthypoglycemic insulin resistance in man is mainly an effect of beta-adrenergic stimulation. J Clin Invest 1987;80:437-42.

66. Pessin JE, Gitomer W, Oka Y, Oppenheimer CL, Czech MP. Beta-adrenergic regulation of insulin and epidermal growth factor receptors in rat adipocytes. J Biol Chem 1983;258:7386-94.

67. Eriksson JW, Lönnroth P, Smith U. Cyclic AMP impairs the rapid effect of insulin to enhance cell-surface insulin-binding capacity in rat adipocytes. Biochem J 1992;288:625-9.

68. Kaestner KH, Flores-Riveros JR, McLenithan JC, Janicot M, Lane MD. Transcriptional repression of the mouse insulin-responsive glucose transporter (GLUT4) gene by cAMP. Proc Natl Acad Sci U S A 1991;88:1933-7.

69. Vannucci SJ, Nishimura H, Satoh S, Cushman SW, Holman GD, Simpson IA. Cell surface accessibility of GLUT4 glucose transporters in insulin- stimulated rat adipose cells. Modulation by isoprenaline and adenosine. Biochem J 1992;288:325-30.

70. Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA. Effect of fatty acids on glucose production and utilization in man. J Clin Invest 1983;72:1737-47.

71. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev 1994;74:761-811.

72. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 1994;79:265-71.

73. Seidell JC, Björntorp P, Sjöström L, Kvist H, Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. Metabolism 1990;39:897-901.

74. Mårin P, Holmäng S, Jönsson L, Sjöström L, Kvist H, Holm G, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes Relat Metab Disord 1992;16:991-7.

75. Cohen JC, Hickman R. Insulin resistance and diminished glucose tolerance in powerlifters ingesting anabolic steroids. J Clin Endocrinol Metab 1987;64:960-3.

76. Paolisso G, Tagliamonte MR, Rizzo MR, Giugliano D. Advancing age and insulin resistance: new facts about an ancient history. Eur J Clin Invest 1999;29:758-69.

77. Kimura M, Tanaka S, Yamada Y, Kiuchi Y, Yamakawa T, Sekihara H. Dehydroepiandrosterone decreases serum tumor necrosis factor-alpha and restores insulin sensitivity: independent effect from secondary weight reduction in genetically obese Zucker fatty rats. Endocrinology 1998;139:3249-53.

78. Lemieux S, Lewis GF, Ben-Chetrit A, Steiner G, Greenblatt EM. Correction of hyperandrogenemia by laparoscopic ovarian cautery in women with polycystic ovarian syndrome is not accompanied by improved insulin sensitivity or lipid-lipoprotein levels. J Clin Endocrinol Metab 1999;84:4278-82.

79. Tripathy D, Shah P, Lakshmy R, Reddy KS. Effect of testosterone replacement on whole body glucose utilisation and other cardiovascular risk factors in males with idiopathic hypogonadotrophic hypogonadism. Horm Metab Res 1998;30:642-5.

80. Johannsson G, Bengtsson BA. Growth hormone and the metabolic syndrome. J Endocrinol Invest 1999;22 (Suppl 5):41-6.

81. Scacchi M, Pincelli AI, Cavagnini F. Growth hormone in obesity. Int J Obes Relat Metab Disord 1999;23:260-71.

82. Fowelin J, Attvall S, von Schenck H, Smith U, Lager I. Characterization of the insulin-antagonistic effect of growth hormone in man. Diabetologia 1991;34:500-6.

83. Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA. Growth hormone-deficient adults are insulin-resistant. Metabolism 1995;44:1126-9.

84. Johannsson G, Mårin P, Lönn L, Ottosson M, Stenlöf K, Björntorp P, et al. Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. J Clin Endocrinol Metab 1997;82:727-34.

85. Rasmussen MH, Hvidberg A, Juul A, Main KM, Gotfredsen A, Skakkebaek NE, et al. Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor-I levels in obese subjects [published erratum appears in J Clin Endocrinol Metab 1995 Aug;80:2446]. J Clin Endocrinol Metab 1995;80:1407-15.

86. Christopher M, Hew FL, Oakley M, Rantzau C, Alford F. Defects of insulin action and skeletal muscle glucose metabolism in growth hormone-deficient adults persist after 24 months of recombinant human growth hormone therapy. J Clin Endocrinol Metab 1998;83:1668-81.

87. Laviades C, Gil MJ, Monreal I, Gonzalez A, Diez J. Tissue availability of insulin-like growth factor I is inversely related to insulin resistance in essential hypertension: effects of angiotensin converting enzyme inhibition. J Hypertens 1998;16:863-70.

88. Chong PK, Jung RT, Bartlett WA, Browning MC. The acute effects of corticotropin-releasing factor on energy expenditure in lean and obese women. Int J Obes Relat Metab Disord 1992;16:529-34.

89. Olster DH, Ferin M. Corticotropin-releasing hormone inhibits gonadotropin secretion in the ovariectomized rhesus monkey. J Clin Endocrinol Metab 1987;65:262-7.

90. Raza J, Massoud AF, Hindmarsh PC, Robinson IC, Brook CG. Direct effects of corticotrophin-releasing hormone on stimulated growth hormone secretion. Clin Endocrinol 1998;48:217-22.
91. Rebuffé-Scrive M, Brönnegård M, Nilsson A, Eldh J, Gustafsson JA, Björntorp P. Steroid hormone receptors in human adipose tissues. J Clin Endocrinol Metab 1990;71:1215-9.
92. Appel B, Fried SK. Effects of insulin and dexamethasone on lipoprotein lipase in human adipose tissue. Am J Physiol 1992;262:E695-9.
93. Rebuffé-Scrive M, Mårin P, Björntorp P. Effect of testosterone on abdominal adipose tissue in men. Int J Obes 1991;15:791-5.
94. Ottosson M, Vikman-Adolfsson K, Enerbäck S, Elander A, Björntorp P, Edén S. Growth hormone inhibits lipoprotein lipase activity in human adipose tissue. J Clin Endocrinol Metab 1995;80:936-41.
95. Rebuffe-Scrive M, Andersson B, Olbe L, Björntorp P. Metabolism of adipose tissue in intraabdominal depots of nonobese men and women. Metabolism 1989;38:453-8.
96. West DB, Prinz WA, Greenwood MR. Regional changes in adipose tissue blood flow and metabolism in rats after a meal. Am J Physiol 1989;257:711-6.
97. Bolinder J, Kager L, Östman J, Arner P. Differences at the receptor and postreceptor levels between human omental and subcutaneous adipose tissue in the action of insulin on lipolysis. Diabetes 1983;32:117-23.
98. Yang S, Xu X, Björntorp P, Edén S. Additive effects of growth hormone and testosterone on lipolysis in adipocytes of hypophysectomized rats. J Endocrinol 1995;147:147-52.
99. Landau BR, Wahren J, Previs SF, Ekberg K, Chandramouli V, Brunengraber H. Glycerol production and utilization in humans: sites and quantitation. Am J Physiol 1996;271:1110-7.
100. Jensen MD. Lipolysis: contribution from regional fat. Annu Rev Nutr 1997;17:127-39.
101. Svedberg J, Strömblad G, Wirth A, Smith U, Björntorp P. Fatty acids in the portal vein of the rat regulate hepatic insulin clearance. J Clin Invest 1991;88:2054-8.
102. Hennes MM, Shrago E, Kissebah AH. Receptor and postreceptor effects of free fatty acids (FFA) on hepatocyte insulin dynamics. Int J Obes 1990;14:831-41.
103. Svedberg J, Björntorp P, Lönnroth P, Smith U. Prevention of inhibitory effect of free fatty acids on insulin binding and action in isolated rat hepatocytes by etomoxir. Diabetes 1991;40:783-6.
104. Peiris AN, Mueller RA, Struve MF, Smith GA, Kissebah AH. Relationship of androgenic activity to splanchnic insulin metabolism and peripheral glucose utilization in premenopausal women. J Clin Endocrinol Metab 1987;64:162-9.
105. Olefsky JM. Decreased insulin binding to adipocytes and circulating monocytes from obese subjects. J Clin Invest 1976;57:1165-72.

106. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.

107. Gordon T, Kannel WB. Obesity and cardiovascular diseases: the Framingham study. Clin Endocrinol Metab 1976;5:367-75.

108. Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr. Diabetes 1987;36:523-34.

109. Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501-13.

110. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961-9.

111. Modan M, Karasik A, Halkin H, Fuchs Z, Lusky A, Shitrit A, et al. Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response. The Israel study of glucose intolerance, obesity and hypertension. Diabetologia 1986;29:82-9.

112. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study. Diabetologia 1999;42:139-45.

113. Mikines KJ. The influence of physical activity and inactivity on insulin action and secretion in man. Acta Physiol Scand Suppl 1992;609:1-43.

114. Wilding J, Williams G. Diabetes and obesity. In: Kopelman PG, Stock MJ, editors. Clinical obesity. Cambridge: Blackwell Science Ltd; 1998. p. 308-49.

115. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM [published erratum appears in Diabetes 1997 Mar;46:536]. Diabetes 1997;46:3-10.

116. Groop LC, Bonadonna RC, Simonson DC, Petrides AS, Shank M, DeFronzo RA. Effect of insulin on oxidative and nonoxidative pathways of free fatty acid metabolism in human obesity. Am J Physiol 1992;263:E79-84.

117. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. Diabetes Care 1992;15:318-68.

118. Yki-Järvinen H. Glucose toxicity. Endocr Rev 1992;13:415-31.

119. Laakso M, Edelman SV, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. A novel mechanism for insulin resistance. J Clin Invest 1990;85:1844-52.

120. Lithell H, Lindgarde F, Hellsing K, Lundqvist G, Nygaard E, Vessby B, et al. Body weight, skeletal muscle morphology, and enzyme activities in relation to fasting serum insulin concentration and glucose tolerance in 48-year-old men. Diabetes 1981;30:19-25.
121. Krotkiewski M, Björntorp P. Muscle tissue in obesity with different distribution of adipose tissue. Effects of physical training. Int J Obes 1986;10:331-41.
122. Lillioja S, Young AA, Culter CL, Ivy JL, Abbott WG, Zawadzki JK, et al. Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. J Clin Invest 1987;80:415-24.
123. Laakso M, Edelman SV, Olefsky JM, Brechtel G, Wallace P, Baron AD. Kinetics of in vivo muscle insulin-mediated glucose uptake in human obesity. Diabetes 1990;39:965-74.
124. Cohen B, Novick D, Rubinstein M. Modulation of insulin activities by leptin. Science 1996;274:1185-8.
125. Hotamisligil GS. The role of TNFalpha and TNF receptors in obesity and insulin resistance. J Intern Med 1999;245:621-5.
126. Tsigos C, Kyrou I, Chala E, Tsapogas P, Stavridis JC, Raptis SA, et al. Circulating tumor necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. Metabolism 1999;48:1332-5.
127. Symonds B. Blood pressure of healty men and women. JAMA 1923;8:232.
128. Kannel WB, Brand N, Skinner JJ, Jr., Dawber TR, McNamara PM. The relation of adiposity to blood pressure and development of hypertension. The Framingham study. Ann Intern Med 1967;67:48-59.
129. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. JAMA 1978;240:1607-10.
130. Donahue RP, Abbott RD, Bloom E, Reed DM, Yano K. Central obesity and coronary heart disease in men. Lancet 1987;1:821-4.
131. Landsberg L. Obesity and hypertension: experimental data. J Hypertens 1992;10(Suppl):195-201.
132. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, et al. Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. J Clin Invest 1985;75:809-17.
133. Feskens EJ, Tuomilehto J, Stengard JH, Pekkanen J, Nissinen A, Kromhout D. Hypertension and overweight associated with hyperinsulinaemia and glucose tolerance: a longitudinal study of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetologia 1995;38:839-47.
134. Brands MW, Hall JE, Keen HL. Is insulin resistance linked to hypertension? Clin Exp Pharmacol Physiol 1998;25:70-6.

135. Hall JE, Brands MW, Henegar JR, Shek EW. Abnormal kidney function as a cause and a consequence of obesity hypertension. Clin Exp Pharmacol Physiol 1998;25:58-64.
136. Landsberg L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med 1986;61:1081-90.
137. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities--the role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996;334:374-81.
138. Rahn KH, Barenbrock M, Hausberg M. The sympathetic nervous system in the pathogenesis of hypertension. J Hypertens 1999;17(Suppl 3):11-4.
139. Salomaa VV, Strandberg TE, Vanhanen H, Naukkarinen V, Sarna S, Miettinen TA. Glucose tolerance and blood pressure: long term follow up in middle aged men [published erratum appears in BMJ 1991 Apr 20;302:939]. BMJ 1991;302:493-6.
140. Salonen JT, Lakka TA, Lakka HM, Valkonen VP, Everson SA, Kaplan GA. Hyperinsulinemia is associated with the incidence of hypertension and dyslipidemia in middle-aged men. Diabetes 1998;47:270-5.
141. Tsutsu N, Nunoi K, Kodama T, Nomiyama R, Iwase M, Fujishima M. Lack of association between blood pressure and insulin in patients with insulinoma. J Hypertens 1990;8:479-82.
142. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. J Clin Invest 1994;94:1172-9.
143. Sartori C, Scherrer U. Insulin, nitric oxide and the sympathetic nervous system: at the crossroads of metabolic and cardiovascular regulation. J Hypertens 1999;17:1517-25.
144. Petrie JR, Ueda S, Webb DJ, Elliott HL, Connell JM. Endothelial nitric oxide production and insulin sensitivity. A physiological link with implications for pathogenesis of cardiovascular disease. Circulation 1996;93:1331-3.
145. Dunbar JC, Hu Y, Lu H. Intracerebroventricular leptin increases lumbar and renal sympathetic nerve activity and blood pressure in normal rats. Diabetes 1997;46:2040-3.
146. Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. Hypertension 1998;31:409-14.
147. DeFronzo RA. The effect of insulin on renal sodium metabolism. A review with clinical implications. Diabetologia 1981;21:165-71.
148. Rocchini AP, Katch V, Kveselis D, Moorehead C, Martin M, Lampman R, et al. Insulin and renal sodium retention in obese adolescents. Hypertension 1989;14:367-74.
149. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. Am J Hypertens 1996;9:746-52.

150. Vierhapper H, Waldhausl W, Nowotny P. The effect of insulin on the rise in blood pressure and plasma aldosterone after angiotensin II in normal man. Clin Sci 1983;64:383-6.

151. Goodfriend TL, Kelley DE, Goodpaster BH, Winters SJ. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. Obes Res 1999;7:355-62.

152. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.

153. Cruz AB, Amatuzio DS, Grande F, Hay LJ. Effect of intraarterial insulin on tissue cholesterol and fatty acids in alloxan-diabetic dogs. Circ Res 1961;9:39-43.

154. Lever AF. Slow pressor mechanisms in hypertension: a role for hypertrophy of resistance vessels? J Hypertens 1986;4:515-24.

155. Schein M, Wittmann DH, Aprahamian CC, Condon RE. The abdominal compartment syndrome: the physiological and clinical consequences of elevated intra-abdominal pressure. J Am Coll Surg 1995;180:745-53.

156. Bloomfield GL, Ridings PC, Blocher CR, Marmarou A, Sugerman HJ. A proposed relationship between increased intra-abdominal, intrathoracic, and intracranial pressure. Crit Care Med 1997;25:496-503.

157. Bloomfield GL, Blocher CR, Fakhry IF, Sica DA, Sugerman HJ. Elevated intra-abdominal pressure increases plasma renin activity and aldosterone levels. J Trauma 1997;42:997-1005.

158. Doty JM, Saggi BH, Sugerman HJ, Blocher CR, Pin R, Fakhry I, et al. Effect of increased renal venous pressure on renal function. J Trauma 1999;47:1000-3.

159. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497-511.

160. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation 1990;82:495-506.

161. Krauss RM. Heterogeneity of plasma low-density lipoproteins and atherosclerosis risk. Curr Opin Lipidol 1994;5:339-49.

162. Laakso M, Sarlund H, Mykkanen L. Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance. Arteriosclerosis 1990;10:223-31.

163. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. J Clin Invest 1993;92:141-6.

164. Ferrannini E, Galvan AQ, Gastaldelli A, Camastra S, Sironi AM, Toschi E, et al. Insulin: new roles for an ancient hormone. Eur J Clin Invest 1999;29:842-52.
165. Williams KJ, Tabas I. The response-to-retention hypothesis of atherogenesis reinforced. Curr Opin Lipidol 1998;9:471-4.
166. Boquist S, Ruotolo G, Tang R, Björkegren J, Bond MG, de Faire U, et al. Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men. Circulation 1999;100:723-8.
167. Hodis HN, Mack WJ. Triglyceride-rich lipoproteins and the progression of coronary artery disease. Curr Opin Lipidol 1995;6:209-14.
168. Hodis HN, Mack WJ, Krauss RM, Alaupovic P. Pathophysiology of triglyceride-rich lipoproteins in atherothrombosis: clinical aspects. Clin Cardiol 1999;22(6 Suppl):II15-20.
169. Powell LM, Wallis SC, Pease RJ, Edwards YH, Knott TJ, Scott J. A novel form of tissue-specific RNA processing produces apolipoprotein- B48 in intestine. Cell 1987;50:831-40.
170. Karpe F, Hellenius ML, Hamsten A. Differences in postprandial concentrations of very-low-density lipoprotein and chylomicron remnants between normotriglyceridemic and hypertriglyceridemic men with and without coronary heart disease. Metabolism 1999;48:301-7.
171. Cohn JS, Johnson EJ, Millar JS, Cohn SD, Milne RW, Marcel YL, et al. Contribution of apoB-48 and apoB-100 triglyceride-rich lipoproteins (TRL) to postprandial increases in the plasma concentration of TRL triglycerides and retinyl esters. J Lipid Res 1993;34:2033-40.
172. Groop LC, Saloranta C, Shank M, Bonadonna RC, Ferrannini E, DeFronzo RA. The role of free fatty acid metabolism in the pathogenesis of insulin resistance in obesity and noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1991;72:96-107.
173. Malmström R, Packard CJ, Watson TD, Rannikko S, Caslake M, Bedford D, et al. Metabolic basis of hypotriglyceridemic effects of insulin in normal men. Arterioscler Thromb Vasc Biol 1997;17:1454-64.
174. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986;232:34-47.
175. Blankenhorn DH, Hodis HN. George Lyman Duff Memorial Lecture. Arterial imaging and atherosclerosis reversal. Arterioscler Thromb 1994;14:177-92.
176. Patsch JR. Postprandial lipaemia. Baillières Clin Endocrinol Metab 1987;1:551-80.
177. Björkegren J, Packard CJ, Hamsten A, Bedford D, Caslake M, Foster L, et al. Accumulation of large very low density lipoprotein in plasma during intravenous infusion of a chylomicron-like triglyceride emulsion reflects competition for a common lipolytic pathway. J Lipid Res 1996;37:76-86.

178. Karpe F. Postprandial lipoprotein metabolism and atherosclerosis. J Intern Med 1999;246:341-55.
179. Windler E, Greeve J, Robenek H, Rinninger F, Greten H, Jäckle S. Differences in the mechanisms of uptake and endocytosis of small and large chylomicron remnants by rat liver. Hepatology 1996;24:344-51.
180. Boren J, Olin K, Lee I, Chait A, Wight TN, Innerarity TL. Identification of the principal proteoglycan-binding site in LDL. A single-point mutation in apo-B100 severely affects proteoglycan interaction without affecting LDL receptor binding. J Clin Invest 1998;101:2658-64.
181. Alaupovic P. David Rubinstein Memorial Lecture: the biochemical and clinical significance of the interrelationship between very low density and high density lipoproteins. Can J Biochem 1981;59:565-79.
182. Blankenhorn DH, Alaupovic P, Wickham E, Chin HP, Azen SP. Prediction of angiographic change in native human coronary arteries and aortocoronary bypass grafts. Lipid and nonlipid factors. Circulation 1990;81:470-6.
183. Hodis HN, Mack WJ, Azen SP, Alaupovic P, Pogoda JM, LaBree L, et al. Triglyceride- and cholesterol-rich lipoproteins have a differential effect on mild/moderate and severe lesion progression as assessed by quantitative coronary angiography in a controlled trial of lovastatin. Circulation 1994;90:42-9.
184. Rigotti A, Krieger M. Getting a handle on "good" cholesterol with the high-density lipoprotein receptor. N Engl J Med 1999;341:2011-3.
185. Rader DJ. Pathophysiology and management of low high-density lipoprotein cholesterol. Am J Cardiol 1999;83:22F-4F.
186. Després JP, Marette A. Relation of components of insulin resistance syndrome to coronary disease risk. Curr Opin Lipidol 1994;5:274-89.
187. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. Science 1996;271:518-20.
188. Arai T, Wang N, Bezouevski M, Welch C, Tall AR. Decreased atherosclerosis in heterozygous low density lipoprotein receptor-deficient mice expressing the scavenger receptor BI transgene. J Biol Chem 1999;274:2366-71.
189. Trigatti B, Rayburn H, Vinals M, Braun A, Miettinen H, Penman M, et al. Influence of the high density lipoprotein receptor SR-BI on reproductive and cardiovascular pathophysiology. Proc Natl Acad Sci U S A 1999;96:9322-7.
190. Duverger N, Kruth H, Emmanuel F, Caillaud JM, Viglietta C, Castro G, et al. Inhibition of atherosclerosis development in cholesterol-fed human apolipoprotein A-I-transgenic rabbits. Circulation 1996;94:713-7.

191. Miyazaki A, Sakuma S, Morikawa W, Takiue T, Miake F, Terano T, et al. Intravenous injection of rabbit apolipoprotein A-I inhibits the progression of atherosclerosis in cholesterol-fed rabbits. Arterioscler Thromb Vasc Biol 1995;15:1882-8.

192. Tangirala RK, Tsukamoto K, Chun SH, Usher D, Pure E, Rader DJ. Regression of atherosclerosis induced by liver-directed gene transfer of apolipoprotein A-I in mice. Circulation 1999;100:1816-22.

193. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45.

194. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410-8.

195. Lichtenstein L, Scott HW, Levin MH. Pathologic changes in gout. Am J Pathol 1956;32:871-7.

196. Hall AP, Barry PE, Dawber TR, McNamara PM. Epidemiology of gout and hyperuricemia. A long-term population study. Am J Med 1967;42:27-37.

197. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. Coronary Artery Risk Development in Young Adults. Ann Epidemiol 1998;8:250-61.

198. Braghiroli A, Sacco C, Erbetta M, Ruga V, Donner CF. Overnight urinary uric acid: creatinine ratio for detection of sleep hypoxemia. Validation study in chronic obstructive pulmonary disease and obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure. Am Rev Respir Dis 1993;148:173-8.

199. Mathru M, Dries DJ, Barnes L, Tonino P, Sukhani R, Rooney MW. Tourniquet-induced exsanguination in patients requiring lower limb surgery. An ischemia-reperfusion model of oxidant and antioxidant metabolism. Anesthesiology 1996;84:14-22.

200. Bardenheuer HJ, Fabry A, Hofling B, Peter K. Adenosine: a sensitive marker of myocardial ischaemia in man. Cardiovasc Res 1994;28:656-62.

201. McCord JM, Fridovich I. The reduction of cytochrome c by milk xanthine oxidase. J Biol Chem 1968;243:5753-60.

202. Terada LS, Guidot DM, Leff JA, Willingham IR, Hanley ME, Piermattei D, et al. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proc Natl Acad Sci U S A 1992;89:3362-6.

203. Tabayashi K, Suzuki Y, Nagamine S, Ito Y, Sekino Y, Mohri H. A clinical trial of allopurinol (Zyloric) for myocardial protection. J Thorac Cardiovasc Surg 1991;101:713-8.

204. Sluiter W, Pietersma A, Lamers JM, Koster JF. Leukocyte adhesion molecules on the vascular endothelium: their role in the pathogenesis of cardiovascular disease and the mechanisms underlying their expression. J Cardiovasc Pharmacol 1993;22(Suppl 4):37-44.

205. Rajagopalan S, Meng XP, Ramasamy S, Harrison DG, Galis ZS. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J Clin Invest 1996;98:2572-9.

206. Ichimori K, Fukahori M, Nakazawa H, Okamoto K, Nishino T. Inhibition of xanthine oxidase and xanthine dehydrogenase by nitric oxide. Nitric oxide converts reduced xanthine-oxidizing enzymes into the desulfo-type inactive form. J Biol Chem 1999;274:7763-8.

207. Leyva F. Uric acid in cardiovascular disease. Current medical literature Cardiology 1999;18:77-83.

208. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta- analysis. Am J Clin Nutr 1992;56:320-8.

209. Ebrahim S, Smith GD. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions. J Public Health Med 1998;20:441-8.

210. Brown SA, Upchurch S, Anding R, Winter M, Ramirez G. Promoting weight loss in type II diabetes. Diabetes Care 1996;19:613-24.

211. Goldstein DJ. Beneficial health effects of modest weight loss. Int J Obes Relat Metab Disord 1992;16:397-415.

212. Blackburn G. Effect of degree of weight loss on health benefits. Obes Res 1995;3(Suppl 2):211-6.

213. Blair SN, Lee IM. Weight loss and risk of mortality. In: Bray GA, Bouchard C, James WPT, editors. Handbook of obesity. New York: Marcel Dekker; 1998. p. 805-18.

214. Pamuk ER, Williamson DF, Serdula MK, Madans J, Byers TE. Weight loss and subsequent death in a cohort of U.S. adults. Ann Intern Med 1993;119:744-8.

215. Lee IM, Paffenbarger RS, Jr. Change in body weight and longevity. JAMA 1992;268:2045-9.

216. Higgins M, D'Agostino R, Kannel W, Cobb J, Pinsky J. Benefits and adverse effects of weight loss. Observations from the Framingham Study [published erratum appears in Ann Intern Med 1993 Nov 15;119:1055]. Ann Intern Med 1993;119:758-63.

217. Allison DB, Faith MS, Heo M, Townsend-Butterworth D, Williamson DF. Meta-analysis of the effect of excluding early deaths on the estimated relationship between body mass index and mortality. Obes Res 1999;7:342-54.

218. Safer DJ. Diet, behavior modification, and exercise: a review of obesity treatments from a long-term perspective. South Med J 1991;84:1470-4.

219. French SA, Jeffery RW, Folsom AR, Williamson DF, Byers T. History of intentional and unintentional weight loss in a population- based sample of women aged 55 to 69 years. Obes Res 1995;3:163-70.

220. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective Study Of Intentional Weight Loss and Mortality In Never- Smoking Overweight US White Women Aged 40-64 Years. Am J Epidemiol 1995;141:1128-41.

221. Williamson DF, Pamuk E, Thun M, Flanders D, Heath C, Byers T. Prospective study of intentional weight loss and mortality in overweight men aged 40-64 years (Abstr.). Obesity Research 1997;5(Suppl):94.

222. Allison DB, Zannolli R, Faith MS, Heo M, Pietrobelli A, VanItallie TB, et al. Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. Int J Obes Relat Metab Disord 1999;23:603-11.

223. Barakat HA, Mooney N, O'Brien K, Long S, Khazani PG, Pories W, et al. Coronary heart disease risk factors in morbidly obese women with normal glucose tolerance. Diabetes Care 1993;16:144-9.

224. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes 1999;48:839-47.

225. Wadden TA, Anderson DA, Foster GD. Two-year changes in lipids and lipoproteins associated with the maintenance of a 5% to 10% reduction in initial weight: some findings and some questions. Obes Res 1999;7:170-8.

226. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998;352:167-72.

227. Payne JH, DeWind LT, Commons RR. Metabolic observations in patients with jejunocolic shunts. (1963, classical article). Obes Res 1996;4:304-15.

228. DeWind LT, Payne JH. Intestinal bypass surgery for morbid obesity. Long-term results. JAMA 1976;236:2298-301.

229. O'Leary JP. Gastrointestinal malabsorptive procedures. Am J Clin Nutr 1992;55(2 Suppl):567-70.

230. Pace WG, Martin EW, Jr., Tetirick T, Fabri PJ, Carey LC. Gastric partitioning for morbid obesity. Ann Surg 1979;190:392-400.

231. Pories WJ, Flickinger EG, Meelheim D, Van Rij AM, Thomas FT. The effectiveness of gastric bypass over gastric partition in morbid obesity: consequence of distal gastric and duodenal exclusion. Ann Surg 1982;196:389-99.

232. Gomez CA. Gastroplasty in morbid obesity: a progress report. World J Surg 1981;5:823-8.

233. Bo O, Modalsli O. Gastric banding, a surgical method of treating morbid obesity: preliminary report. Int J Obes 1983;7:493-9.

234. Kuzmak LI. Stoma adjustable silicone gastric banding. In: Nyhus LM, Mason EE, editors. Problems in General surgery. Philadelphia: Lippincott; 1992. p. 298-317.
235. Forsell P, Hallerbäck B, Glise H, Hellers G. Complications following Swedish adjustable gastric banding: a long-term follow-up. Obes Surg 1999;9:11-6.
236. O'Brien PE, Brown WA, Smith A, McMurrick PJ, Stephens M. Prospective study of a laparoscopically placed, adjustable gastric band in the treatment of morbid obesity. Br J Surg 1999;86:113-8.
237. Mason EE. Morbid obesity: use of vertical banded gastroplasty. Surg Clin North Am 1987;67:521-37.
238. Lönroth H, Dalenbäck J, Haglind E, Josefsson K, Olbe L, Fagevik Olsen M, et al. Vertical banded gastroplasty by laparoscopic technique in the treatment of morbid obesity. Surg Laparosc Endosc 1996;6:102-7.
239. Hall JC, Watts JM, O'Brien PE, Dunstan RE, Walsh JF, Slavotinek AH, et al. Gastric surgery for morbid obesity. The Adelaide Study. Ann Surg 1990;211:419-27.
240. Kral JG. Surgical treatment of obesity. In: Kopelman PG, Stock MJ, editors. Clinical obesity. Cambridge: Blackwell Science Ltd; 1998. p. 545-63.
241. Mason EE, Ito C. Gastric bypass in obesity. Surg Clin North Am 1967;47:1345-51.
242. Alden JF. Gastric and jejunoileal bypass. A comparison in the treatment of morbid obesity. Arch Surg 1977;112:799-806.
243. Lönroth H, Dalenbäck J, Haglind E, Lundell L. Laparoscopic gastric bypass. Another option in bariatric surgery. Surg Endosc 1996;10:636-8.
244. Lönroth H. Laparoscopic gastric bypass. Obes Surg 1998;8:563-5.
245. Scopinaro N, Gianetta E, Civalleri D, Bonalumi U, Bachi V. Bilio-pancreatic bypass for obesity: II. Initial experience in man. Br J Surg 1979;66:618-20.
246. Scopinaro N, Adami GF, Marinari GM, Gianetta E, Traverso E, Friedman D, et al. Biliopancreatic diversion. World J Surg 1998;22:936-46.
247. Mason EE. Ileal transposition and enteroglucagon/GLP-1 in obesity (and diabetic?) surgery. Obes Surg 1999;9:223-8.
248. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet 1987:1300-4.
249. Orskov C, Poulsen SS, Moller M, Holst JJ. Glucagon-like peptide I receptors in the subfornical organ and the area postrema are accessible to circulating glucagon-like peptide I. Diabetes 1996;45:832-5.
250. Andersen T, Backer OG, Stokholm KH, Quaade F. Gastroplasty versus very low calorie diet in morbid obesity. Short- term results of a randomized clinical trial. Ugeskr Laeger 1982;144:390-4.
251. Andersen T, Backer OG, Stokholm KH, Quaade F. Randomized trial of diet and gastroplasty compared with diet alone in morbid obesity. N Engl J Med 1984;310:352-6.

252. Andersen T, Stokholm KH, Backer OG, Quaade F. Long-term (5-year) results after either horizontal gastroplasty or very- low-calorie diet for morbid obesity. Int J Obes 1988;12:277-84.

253. Martin LF, Tan TL, Horn JR, Bixler EO, Kauffman GL, Becker DA, et al. Comparison of the costs associated with medical and surgical treatment of obesity. Surgery 1995;118:599-606.

254. Sjöström L, Larsson B, Backman L, Bengtsson C, Bouchard C, Dahlgren S, et al. Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. Int J Obes Relat Metab Disord 1992;16:465-79.

255. Deitel M. Surgery for the morbidly obese patient. Philadelphia: Lea & Febiger; 1989.

256. Maxwell MH, Waks AU, Schroth PC, Karam M, Dornfeld LP. Error in blood-pressure measurement due to incorrect cuff size in obese patients. Lancet 1982;3:33-6.

257. Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation 1968;38:1104-15.

258. Wilhelmsen L, Tibblin G, Aurell M, Bjure J, Ekstrom-Jodal B, Grimby G. Physical activity, physical fitness and risk of myocardial infarction. Adv Cardiol 1976;18:217-30.

259. Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur Heart J 1999;20:269-77.

260. Lindroos AK, Lissner L, Sjöström L. Does degree of obesity influence the validity of reported energy and protein intake? Results from the SOS Dietary Questionnaire. Swedish Obese Subjects. Eur J Clin Nutr 1999;53:375-8.

261. Lindroos AK, Lissner L, Sjöström L. Validity and reproducibility of a self-administered dietary questionnaire in obese and non-obese subjects. Eur J Clin Nutr 1993;47:461-81.

262. Kvist H, Sjöström L, Chowdhury B, Alpsten M, Arvidsson B, Larsson L, et al. Body fat and adipose tissue determinations by computed tomography and by measurements of total body potassium. In: Yasamura S, Harrison JE, McNeill KG, Woodhead AD, Dilmanian FA, editors. Advances in In Vivo Body Composition Studies. New York: Plenum Press; 1990. p. 197-218.

263. Forbes GB, Gallup J, Hursh JB. Estimation of total adipose tissue from potassium -40 content. Science 1961;133:101.

264. Kvist H, Chowdhury B, Grangard U, Tylén U, Sjöström L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. Am J Clin Nutr 1988;48:1351-61.

265. Sjöström L. A computer-tomography based multicompartment body composition technique and anthropometric predictions of lean body mass, total and subcutaneous adipose tissue. Int J Obes 1991;15 (Suppl 2):19-30.

266. Feuer EJ, Kessler LG. Test statistic and sample size for a two-sample McNemar test. Biometrics 1989;45:629-36.
267. Kissebah A, Murray A, Murray R, Hartz A, Vydelingum N, Rimm A, et al. Relationship of body fat distribution to glucose tolerance and clinical diabetes in obese women (Abstr.). Clin Res 1980;28:520.
268. Björntorp P. The associations between obesity, adipose tissue distribution and disease. Acta Med Scand 1987;Suppl 723:121-34.
269. Sjöström LV. Morbidity of severely obese subjects. Am J Clin Nutr 1992;55(2 Suppl):508-15.
270. Lönn L, Kvist H, Ernest I, Sjöström L. Changes in body composition and adipose tissue distribution after treatment of women with Cushing's syndrome. Metabolism 1994;43:1517-22.
271. Lönn L, Johansson G, Sjöström L, Kvist H, Odén A, Bengtsson BA. Body composition and tissue distributions in growth hormone deficient adults before and after growth hormone treatment. Obes Res 1996;4:45-54.
272. Brummer RJ, Lönn L, Kvist H, Grangård U, Bengtsson BA, Sjöström L. Adipose tissue and muscle volume determination by computed tomography in acromegaly, before and 1 year after adenomectomy. Eur J Clin Invest 1993;23:199-205.
273. Dahlberg G. Statistical methods for medical and biological students. London: Allen & Unwin; 1948.
274. Chowdhury B, Lantz H, Sjöström L. Computed tomography-determined body composition in relation to cardiovascular risk factors in Indian and matched Swedish males. Metabolism 1996;45:634-44.
275. van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Visser M. Abdominal diameters as indicators of visceral fat: comparison between magnetic resonance imaging and anthropometry. Br J Nutr 1993;70:47-58.
276. Svendsen OL, Hassager C, Bergmann I, Christiansen C. Measurement of abdominal and intra-abdominal fat in postmenopausal women by dual energy X-ray absorptiometry and anthropometry: comparison with computerized tomography. Int J Obes Relat Metab Disord 1993;17:45-51.
277. Chowdhury B, Kvist H, Andersson B, Björntorp P, Sjöström L. CT-determined changes in adipose tissue distribution during a small weight reduction in obese males. Int J Obes Relat Metab Disord 1993;17:685-91.
278. van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Droop A, Bakker CJ. Waist-hip ratio is a poor predictor of changes in visceral fat. Am J Clin Nutr 1993;57:327-33.
279. Ross R, Rissanen J, Hudson R. Sensitivity associated with the identification of visceral adipose tissue levels using waist circumference in men and women: effects of weight loss. Int J Obes Relat Metab Disord 1996;20:533-8.

280. Borkan GA, Hults DE, Gerzof SG, Robbins AH, Silbert CK. Age changes in body composition revealed by computed tomography. J Gerontol 1983;38:673-7.

281. Lemieux S, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, Despres JP. Seven-year changes in body fat and visceral adipose tissue in women. Association with indexes of plasma glucose-insulin homeostasis. Diabetes Care 1996;19:983-91.

282. Janssen I, Ross R. Effects of sex on the change in visceral, subcutaneous adipose tissue and skeletal muscle in response to weight loss. Int J Obes Relat Metab Disord 1999;23:1035-46.

283. Smith SR, Zachwieja JJ. Visceral adipose tissue: a critical review of intervention strategies. Int J Obes Relat Metab Disord 1999;23:329-35.

284. Davis BR, Blaufox MD, Oberman A, Wassertheil-Smoller S, Zimbaldi N, Cutler JA, et al. Reduction in long-term antihypertensive medication requirements. Effects of weight reduction by dietary intervention in overweight persons with mild hypertension. Arch Intern Med 1993;153:1773-82.

285. Carson JL, Ruddy ME, Duff AE, Holmes NJ, Cody RP, Brolin RE. The effect of gastric bypass surgery on hypertension in morbidly obese patients. Arch Intern Med 1994;154:193-200.

286. Foley EF, Benotti PN, Borlase BC, Hollingshead J, Blackburn GL. Impact of gastric restrictive surgery on hypertension in the morbidly obese. Am J Surg 1992;163:294-7.

287. Schotte DE, Stunkard AJ. The effects of weight reduction on blood pressure in 301 obese patients. Arch Intern Med 1990;150:1701-4.

288. Dornfeld LP, Maxwell MH, Waks AU, Schroth P, Tuck ML. Obesity and hypertension: long-term effects of weight reduction on blood pressure. Int J Obes 1985;9:381-9.

289. Ikeda T, Gomi T, Hirawa N, Sakurai J, Yoshikawa N. Improvement of insulin sensitivity contributes to blood pressure reduction after weight loss in hypertensive subjects with obesity. Hypertension 1996;27:1180-6.

290. Grassi G, Cattaneo BM, Seravalle G, Colombo M, Cavagnini F, Mancia G. Obesity and the sympathetic nervous system. Blood Press Suppl 1996;1:43-6.

291. Rosmond R, Björntorp P. Blood pressure in relation to obesity, insulin and the hypothalamic- pituitary-adrenal axis in Swedish men. J Hypertens 1998;16:1721-6.

292. Sonne-Holm S, Sørensen TI, Jensen G, Schnohr P. Independent effects of weight change and attained body weight on prevalence of arterial hypertension in obese and non-obese men. BMJ 1989;299:767-70.

293. Ernsberger P, Koletsky RJ, Kilani A, Viswan G, Bedol D. Effects of weight cycling on urinary catecholamines: sympathoadrenal role in refeeding hypertension. J Hypertens 1998;16:2001-5.

294. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. JAMA 1981;245:1225-9.

295. Kannel WB. Historic perspectives on the relative contributions of diastolic and systolic blood pressure elevation to cardiovascular risk profile. Am Heart J 1999;138:205-10.
296. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Levy D. Differential impact of systolic and diastolic blood pressure level on JNC-VI staging. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 1999;34:381-5.
297. Lee ML, Rosner BA, Vokonas PS, Weiss ST. Longitudinal analysis of adult male blood pressure: The Normative Aging Study, 1963-1992. J Epidemiol Biostat 1996;1:79-87.
298. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. N Engl J Med 2000;342:1-8.
299. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. Circulation 1999;100:354-60.
300. Lee ML, Rosner BA, Weiss ST. Relationship of blood pressure to cardiovascular death: the effects of pulse pressure in the elderly. Ann Epidemiol 1999;9:101-7.
301. London GM, Guerin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. Am Heart J 1999;138:220-4.
302. Franklin SS, Sutton-Tyrrell K, Belle SH, Weber MA, Kuller LH. The importance of pulsatile components of hypertension in predicting carotid stenosis in older adults. J Hypertens 1997;15:1143-50.
303. Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 1998;32:560-4.
304. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension : prognostic information provided by pulse pressure. Hypertension 1999;34:375-80.
305. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Philadelphia, Pa: Lea & Febiger 1998.
306. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. Circulation 1999;100:1387-93.
307. Karason K, Wikstrand J, Sjöström L, Wendelhag I. Weight loss and progression of early atherosclerosis in the carotid artery: a four-year controlled study of obese subjects. Int J Obes Relat Metab Disord 1999;23:948-56.

GÖTEBORGS UNIVERSITET
GÖTEBORGS UNIVERSITETSBIBLIOTEK

Digitaltryckt & Bunden
Vasastadens Bokbinderi AB
2000