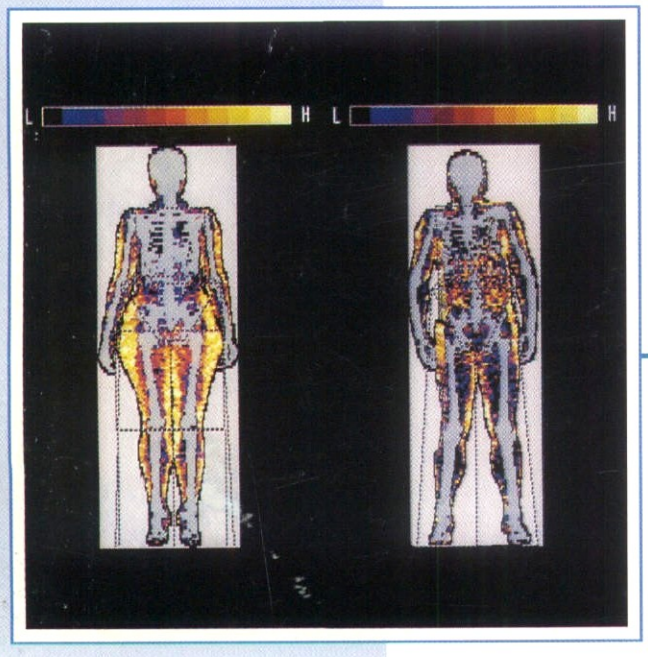
ATLAS

of overweight

body fat distribution



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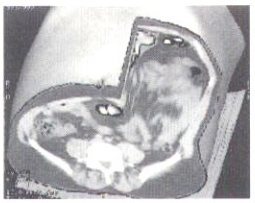
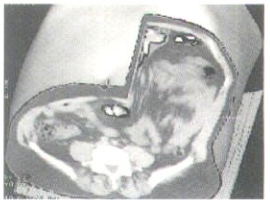
CONTENTS



FOREWORD

Overweight is frequently associated with chronic disorders such as hypertension, diabetes, hyperlipidaemia and cardiovascular disease. Despite these established relationships, the clinician is faced with a diversity among his overweight patients, some of whom show none of the metabolic features associated with an increased risk of complications. The challenge is to identify overweight patients who are at risk and thereby merit closer medical attention. A major contribution to this end was the pioneering work of Jean Vague,[1] conducted in France in the 1940s, which was the first to reveal the importance of body fat topography as an indicator of risk. This was followed by the remarkable contributions of Per Björntorp[2] in Sweden and Ahmed Kissebah[3] in the United States, which have led to the inclusion of regional body fat distribution among established risk factors for cardiovascular disease and its related mortality. Prospective studies have shown that a high proportion of abdominal adipose tissue is associated with an increased risk of developing diabetes and cardiovascular disease. Furthermore, this relationship has been shown to be partly independent of total body fat content.[4]

With the development of imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI), it has been possible to measure precisely the distribution of body fat. Studies assessing fat topography with CT have shown that



the amount of fat located in the abdominal cavity, the so-called visceral adipose tissue, is closely correlated with the metabolic disturbances associated with abdominal overweight.[5] A high proportion of visceral adipose tissue in the presence or absence of overweight increases the risk of metabolic complications. It is therefore of paramount importance for the clinician to consider body fat distribution in the evaluation of the overweight patient. As most physicians do not have access to imaging techniques, it was important to develop anthropometric methods to evaluate abdominal fat deposition. The concurrent use of body mass index (BMI) and waist/hip ratio (WHR) is suggested. Among patients with BMI greater than 25 kg/m^2, WHR values greater than 0.85 in women and greater than 1.00 in men are likely to be associated with a marked accumulation of abdominal fat.[6] Furthermore, we have recently reported that waist circumference alone is a good indicator both of total body fat and of visceral adipose accumulation. We have proposed that a waist circumference of 100 cm and above may indicate the presence of abdominal adipose tissue sufficient to predict an altered risk profile.[7]

The main aim of this atlas is to provide the health professional with a basic outline of the risks of overweight, the importance of regional body fat distribution, the anthropometric approaches to estimating visceral adipose tissue and the therapeutic implications. It is clear from the issues discussed in this volume that our perception of overweight as a medical condition has been more clearly defined and hopefully this will improve our management of patients. Some overweight individuals are not markedly at risk of metabolic complications, while on the other hand, a significant proportion of the population have an excess accumulation of visceral adipose tissue, which, even in the absence of overweight, puts them at risk of developing diabetes and cardiovascular disease. The identification and treatment of these individuals represents an important goal with considerable public health implications.

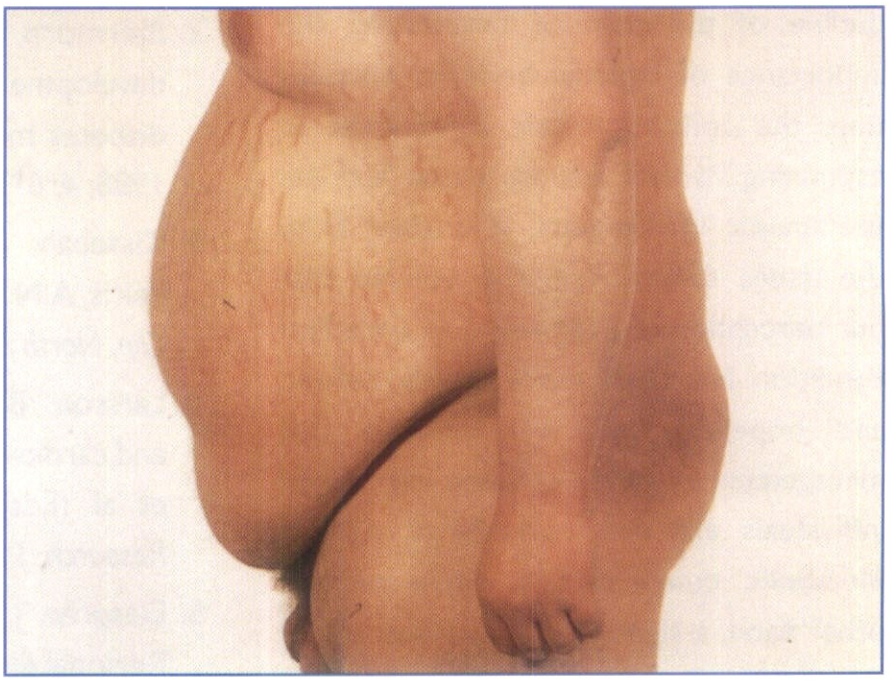
1. Vague, J. *Obesities. John Libbey and Editions Solal, Marseille,* 1991.
2. Björntorp, P. Abdominal obesity and the development of non-insulin dependent diabetes mellitus. *Diabetes Metab. Rev.,* 1988; *4:* 615–622.
3. Kissebah, A.H., Freedman, D.S. and Peiris, A.N. Health risks of obesity. *Med. Clin. North Am.,* 1989; *73:* 111–138.
4. Larsson, B. Obesity, Fat Distribution and cardiovascular disease. Oomura, X. et al (Eds). *Progression in Overweight Research,* 1990, 375–79.
5. Després, J.P., Moorjani, S., Lupien, P.J. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis,* 1990; *10:* 497–511.
6. Després, J.P. Assessing obesity. Beyond BMI. *NIN Review,* 1992; *7:* 1–4.
7. Pouliot, M.C., Després, J.P., Lemieux, S., Moorjani, S., Bouchard, C., Tremblay, A., Nadeau, A. and Lupien, P.J. 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:* 460–468.

Introduction

Overweight is a common condition and its incidence continues to increase. In most cases, overweight is the result of a calorific intake that exceeds the amount of energy expended. The contemporary Western diet, which commonly contains an excess of fat, carbohydrate and calories contributes significantly to the prevalence of this dangerous condition.

Clinicians have known for many years that overweight is a serious risk factor for a variety of medical conditions, including cardiovascular disease, cerebrovascular disease, diabetes mellitus and hyperlipidaemia.

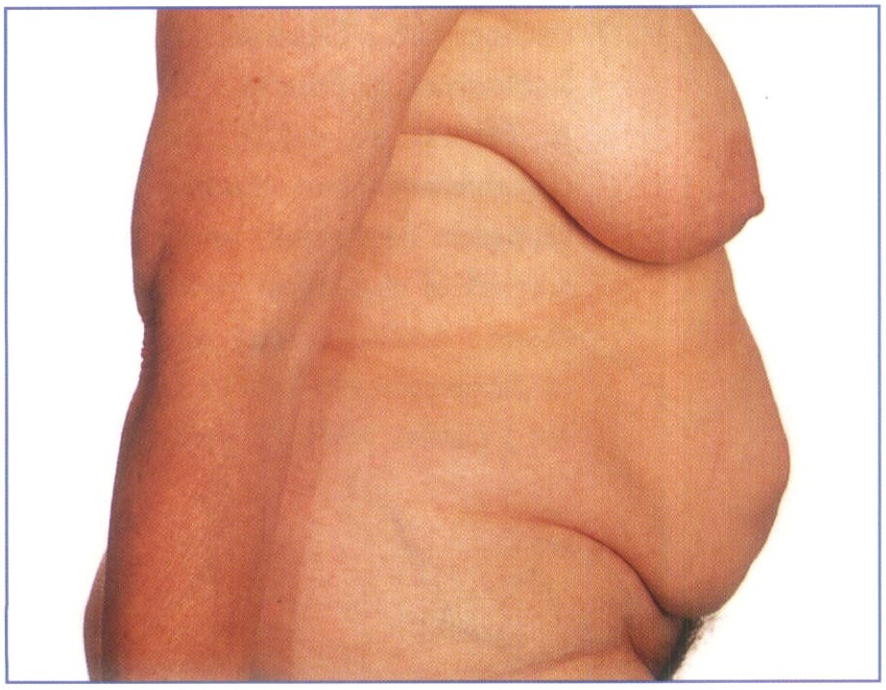
Overweight male subject showing abdominal fat distribution



Courtesy of Leicester Royal Infirmary

Figure 1

Overweight female subject showing abdominal fat distribution



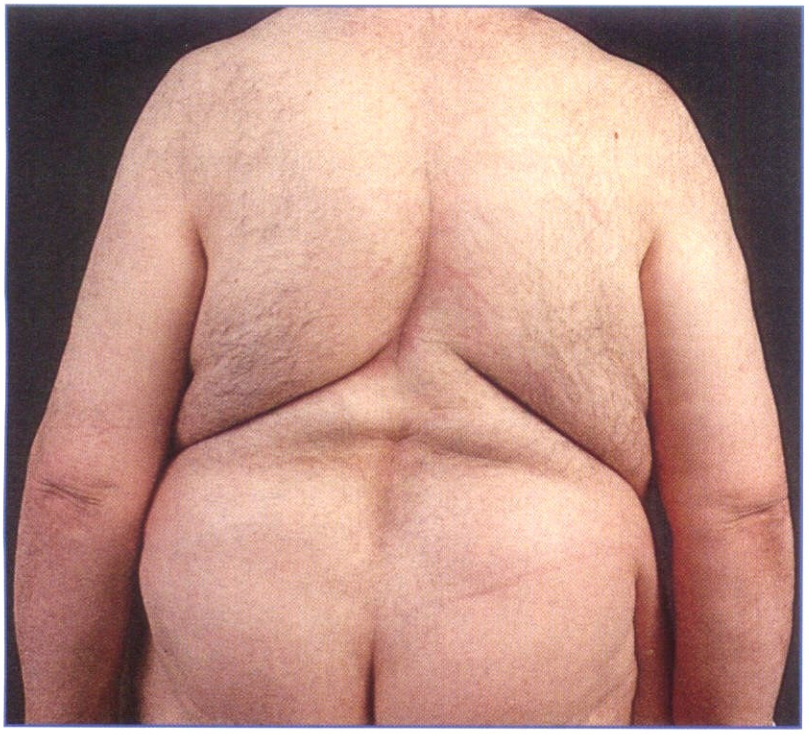
Medical Illustration, South Birmingham Acute Unit

Figure 2

Even a small reduction in body mass can effect a reduction in morbidity and mortality, and therefore the management of food intake with the aid of pharmaceutical intervention offers significant benefit to the overweight subject.

Overweight subjects can be divided into two subpopulations, on the basis of body fat (adipose tissue) distribution. The two broad categories are upper body overweight, as illustrated in Figures 1 and 2, in which the subject's fat is located primarily in the abdominal region, and lower body or gluteofemoral overweight, shown in Figures 3 and 4, in which fat is deposited mainly in the hip and buttock regions. Although upper body fat distribution is more common in men and

Overweight male subject showing gluteofemoral fat distribution



Courtesy of Medical Photography, Luton & Dunstable NHS Trust

Figure 3

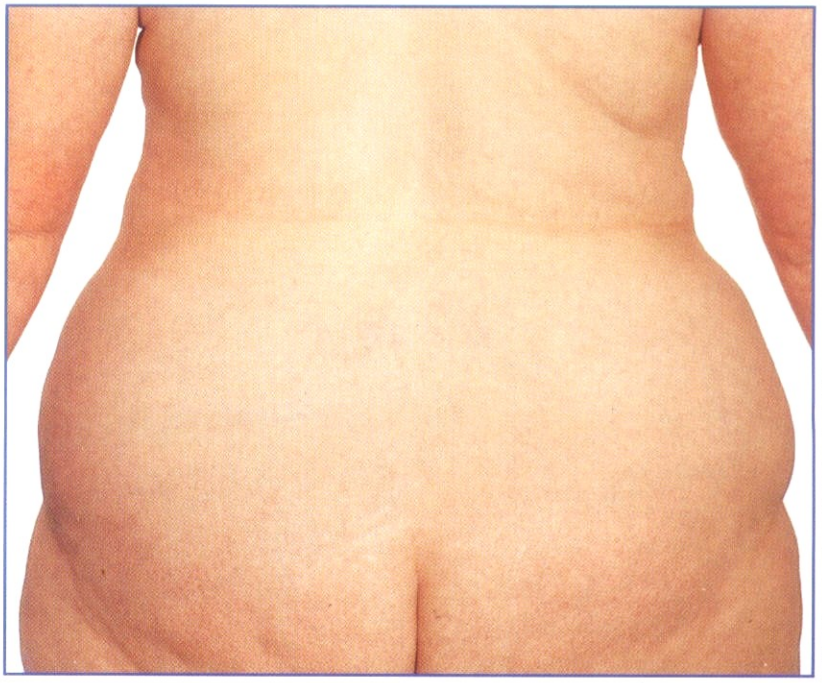
gluteofemoral distribution is found predominantly in women, these photographs illustrate that both types of body fat distribution are found in both male and female subjects.

Although there is a clear link between the degree of adiposity and morbidity[8] and mortality,[9] studies have shown that the *distribution* of body fat also has an important influence on the health risk of overweight, with upper body fat distribution representing more of a threat to health and longevity than lower body fat distribution. Indeed, body fat distribution is a better indicator of cardiovascular disease and cerebrovascular disease than the *extent* of overweight.[10,11]

The abdominal fat depot comprises subcutaneous and visceral (intra-abdominal) components. These two types of abdominal fat possess different morphological and metabolic characteristics, and as described in this publication, there is a strong correlation between the incidence of excess visceral fat and metabolic disorders.

Les laboratoires Servier have produced this Atlas to aid members of the medical profession in the day-to-day management of their overweight subjects. We explore the theme of body fat distribution, highlight the identification of abdominal visceral fat as a risk factor in addition to overweight and describe the valuable role that Adifax can play in the treatment of overweight. As described in Chapter 7, this agent helps to reshape unhealthy eating habits in overweight subjects and is of particular value as it leads to a reduced waist to hip ratio by selectively reducing abdominal visceral fat.

Overweight Female subject showing gluteofemoral fat distribution



Medical Illustration, South Birmingham Acute Unit

Figure 4

8. Van Itallie, T.B. *Ann. Intern. Med.*, 1985; *103:* 983–988.
9. Hubert, H.B., Feinleib, M., McNamara, P.M. and Castelli, W.P. *Circulation,* 1983; *67:* 968–977.
10. Larsson, B., Svärdsudd, K., Welin, L., Wilhelmsen, L., Björntorp, P. and Tibblin, G. *Br. Med. J.,* 1984; *288:* 1401–1404.
11. Lapidus, L., Bengtsson, C., Larsson, B., Pennert, K., Rybo, E. and Sjöström, L. *Br. Med. J.,* 1984; *289:* 1257–1261.

Anthropometry and the Assessment of Fat-Related Health Risks

Several anthropometric measurements have been used to predict the fat-related health risks that a subject may be exposed to.

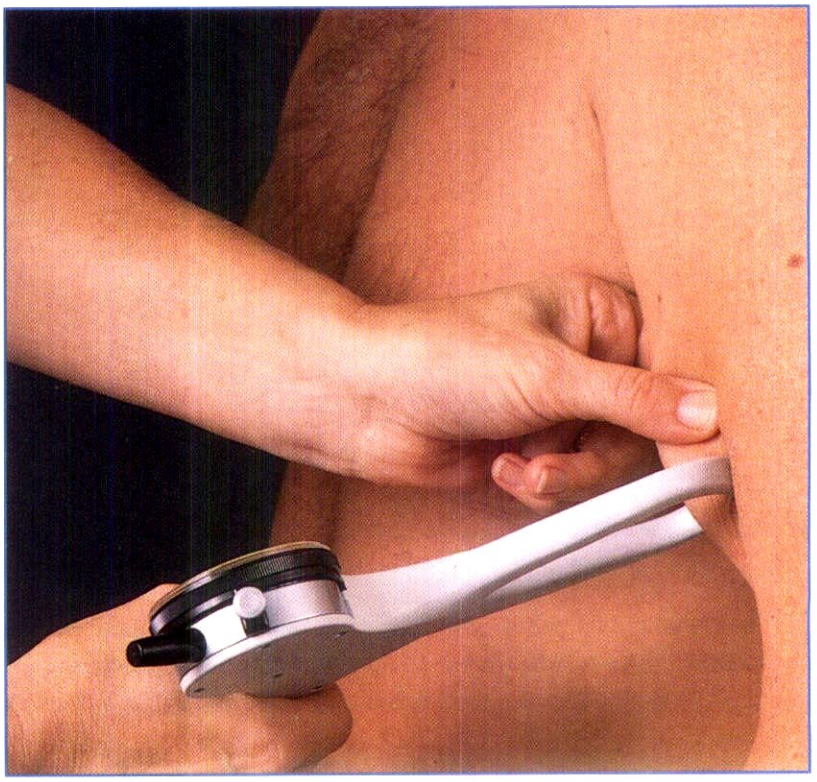
BODY MASS INDEX

Body Mass Index (BMI) is defined as:

$$BMI = \frac{(\text{Weight in kg})}{(\text{Height in metres})^2}$$

BMI values of 19–24 in females and 20–25 in males are associated with the highest long-term life expectancy. The BMI measurement has the advantage of being simple to obtain, and it requires few resources. Its disadvantage is the fact that the reliability of the technique depends on the subject having an average amount of muscle, and BMI does not differentiate between upper and lower body fat distribution.

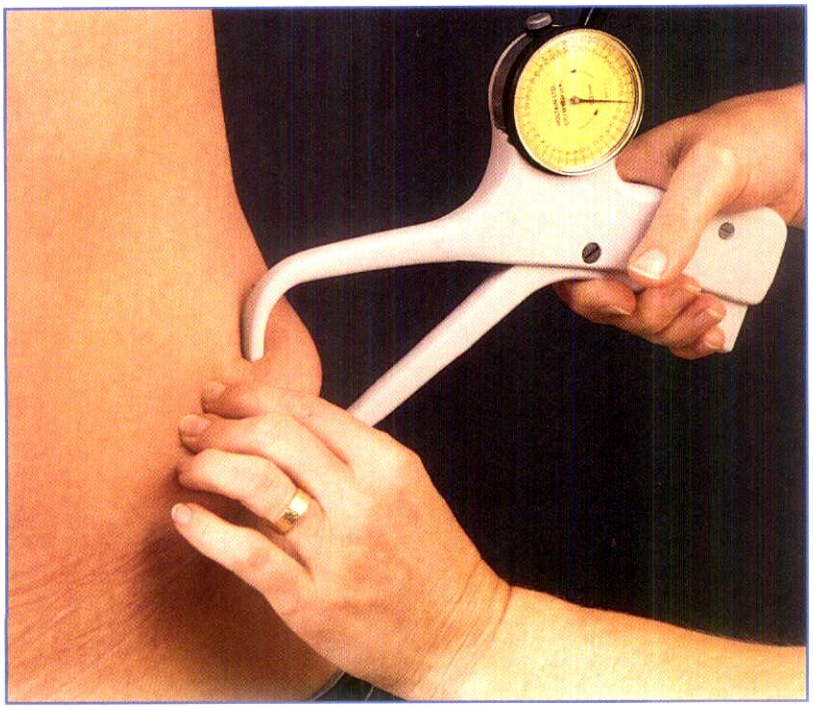
Skinfold measurements in the upper body



Courtesy of Medical Photography, Luton & Dunstable NHS Trust

Figure 5

Skinfold measurements in the lower body



Courtesy of Medical Photography, Luton & Dunstable Hospital NHS Trust

Figure 6

SKINFOLD THICKNESS

Measurement of skinfold thickness (Figures 5 and 6) provides an indication of the amount of subcutaneous fat, and is of greater value than BMI measurements in elderly patients, who have lost muscle as part of the general ageing process, and in muscular subjects. However, the disadvantage of this technique is that reproducible measurements are relatively difficult to obtain and therefore it is not widely used.

Correct measurement of the waist circumference

Dr J Seidell

Figure 7

Correct measurement of the hip circumference

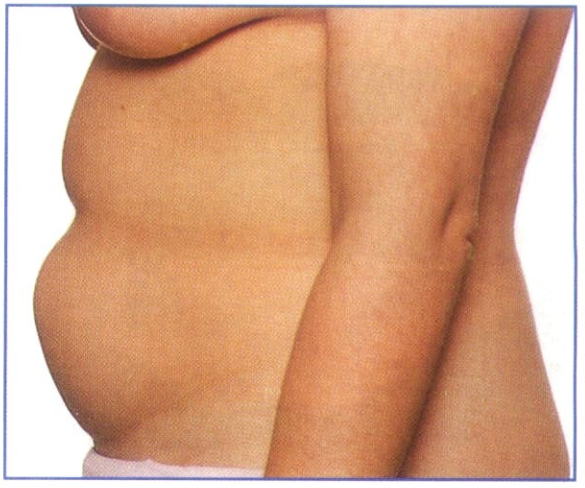
Dr J Seidell

Figure 8

WAIST/HIP RATIO

As described in Section 6, the waist/hip circumference ratio (WHR) is a good indicator of the risk that an overweight subject is exposed to. Upper body overweight is most often defined by a WHR > 0.83 in women and WHR > 0.95 in men. The World Health Organization has published recommendations on the measurement of waist and hip circumferences. The waist circumference is measured midway between the lower rib margin and the iliac crest (Figure 7). The hip circumference is measured over the great trochanters (Figure 8). Despite the proven usefulness of WHR values, accurate waist circumference measurements are difficult to obtain for subjects who are significantly overweight and have no 'waist'.

Slightly overweight subject showing abdominal fat distribution



Medical Illustration, South Birmingham Acute Unit

Figure 9

Figure 9 is a photograph of a slightly overweight subject showing upper body fat distribution. Although the degree of overweight is limited in this case, the predictive value of the WHR value allows the clinician to identify an increased health risk in such a subject.

Types of Adipose Tissue

HYPERPLASTIC/ HYPERTROPHIC

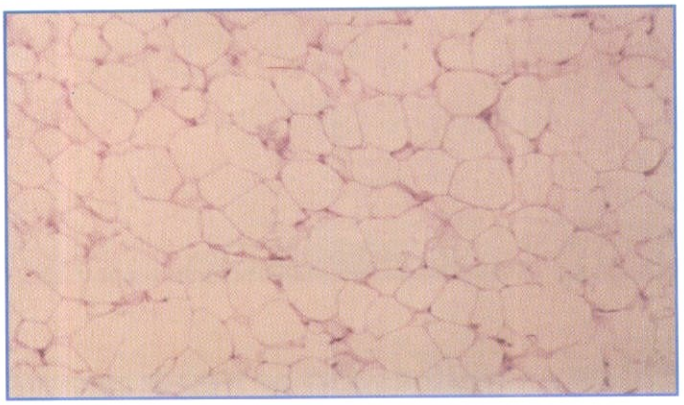
In overweight subjects, the size or number of adipocytes may be increased compared with subjects of average weight. In hyperplastic adipose tissue, the number of adipocytes is increased (Figure 10) and in hypertrophic adipose tissue, the adipocytes are enlarged, mainly due to an increased lipid content (Figure 11). Hypertrophic adipose tissue tends to correlate with upper body fat distribution, and is associated with metabolic disorders such as insulin resistance.

SUBCUTANEOUS/VISCERAL

Abdominal fat is located external to the abdominal wall in the subcutis, or intra-abdominally (Figure 12). Intra-abdominal fat is composed of three different components, namely omental, mesenteric and extraperitoneal fat, which together are referred to as abdominal visceral fat. Omental and mesenteric fat together constitute the intraperitoneal or 'portal' adipose tissue, that is, adipose tissue that is drained by the portal vein.

Figures 13 and 14 show intra-operative views of subcutaneous abdominal fat and visceral abdominal fat, respectively.

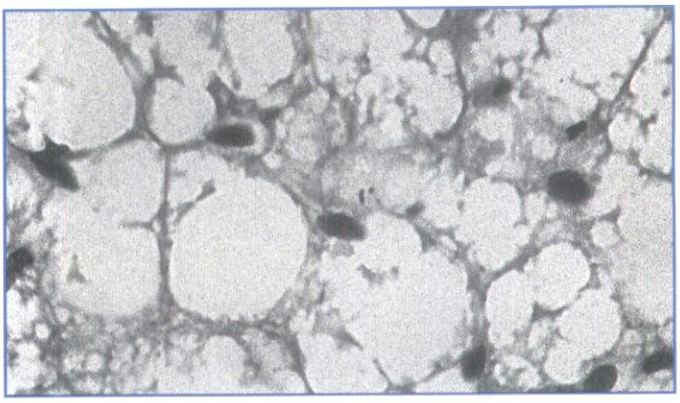
HYPERPLASTIC ADIPOSE TISSUE



Courtesy of Medical Photography, Luton & Dunstable Hospital NHS Trust

Figure 10: (Histological view, x32 magnification.)

HYPERTROPHIC ADIPOSE TISSUE



Courtesy of Professor MEJ Lean

Figure 11: (Histological view, x130 magnification.)

ANATOMY OF ABDOMINAL FAT DEPOSITS

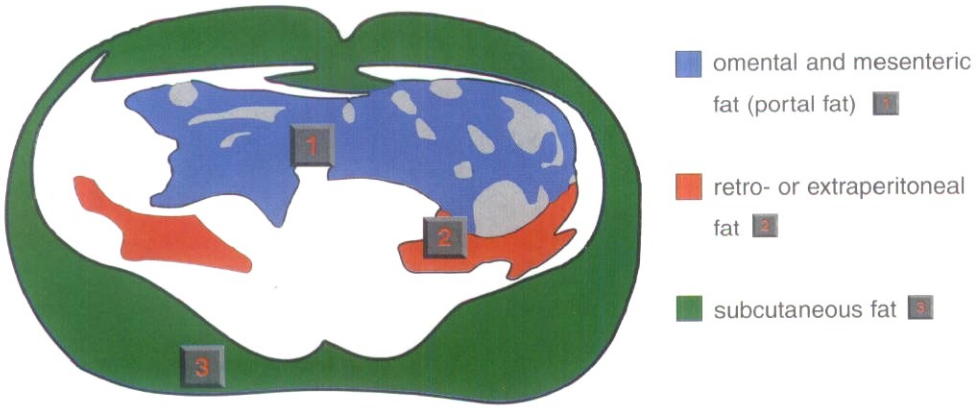


Figure 12: From Van der Kooy and Seidell.[13]

These regions of adipose tissue differ in physical appearance and are composed of different populations of adipocytes. Abdominal visceral adipocytes exhibit a higher turnover of triglycerides. Mobilization of triglycerides from portal adipose tissue leads to elevated levels of free fatty acids (FFAs) in the portal vein, which in turn increases hepatic forma-

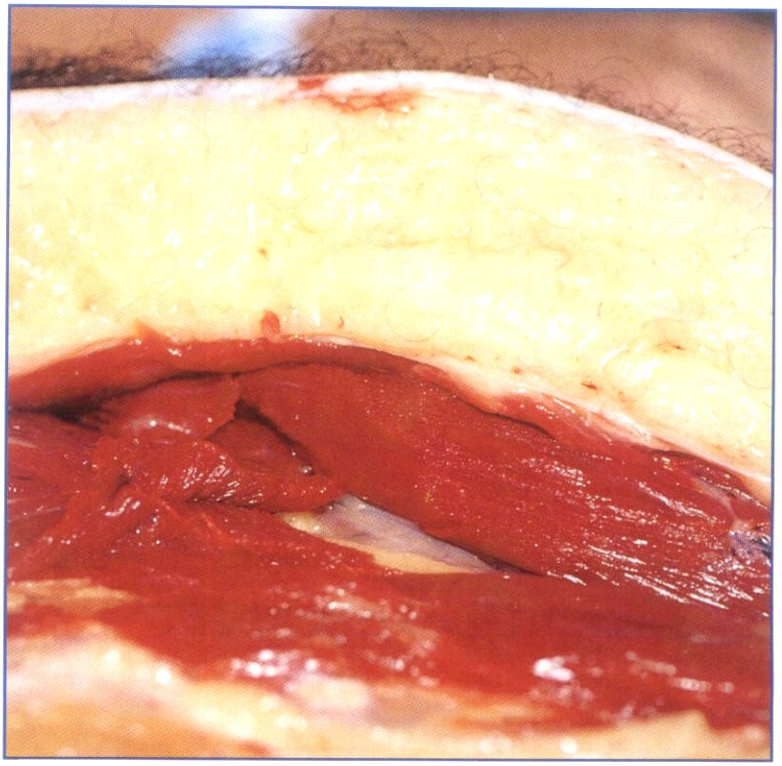
tion of triglycerides and interferes with insulin dynamics. The long-term consequences of increased portal vein FFA concentrations are insulin resistance, increased gluconeogenesis, decreased hepatic insulin clearance and increased hepatic secretion of very-low-density lipoproteins (VLDL).[12] These complications are described in greater detail in Chapter 5.

The surgeon who observes significant amounts of visceral fat during surgery should be aware that the subject is at increased risk of metabolic dysfunction and associated diseases.

12. Björntorp, P. *Diabetes Care,* 1991; *14:* 1132–1143.

13. van der Kooy, K. and Seidell, J.C. *Int. J. Obes.,* 1993; *17:* 187–196.

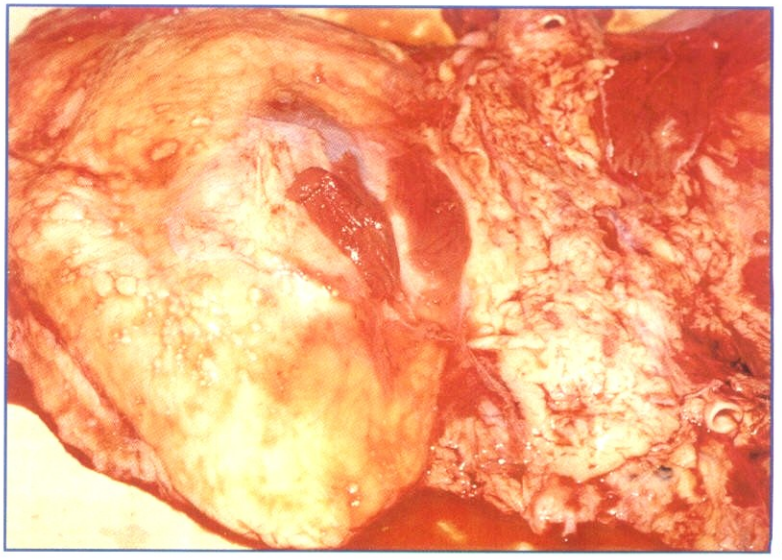
INTRA-OPERATIVE VIEW OF SUBCUTANEOUS ABDOMINAL FAT



Courtesy of Medical Photography, Luton & Dunstable NHS Trust

Figure 13

INTRA-OPERATIVE VIEW OF ABDOMINAL VISCERAL FAT



Courtesy of Medical Photography, Luton & Dunstable NHS Trust

Figure 14

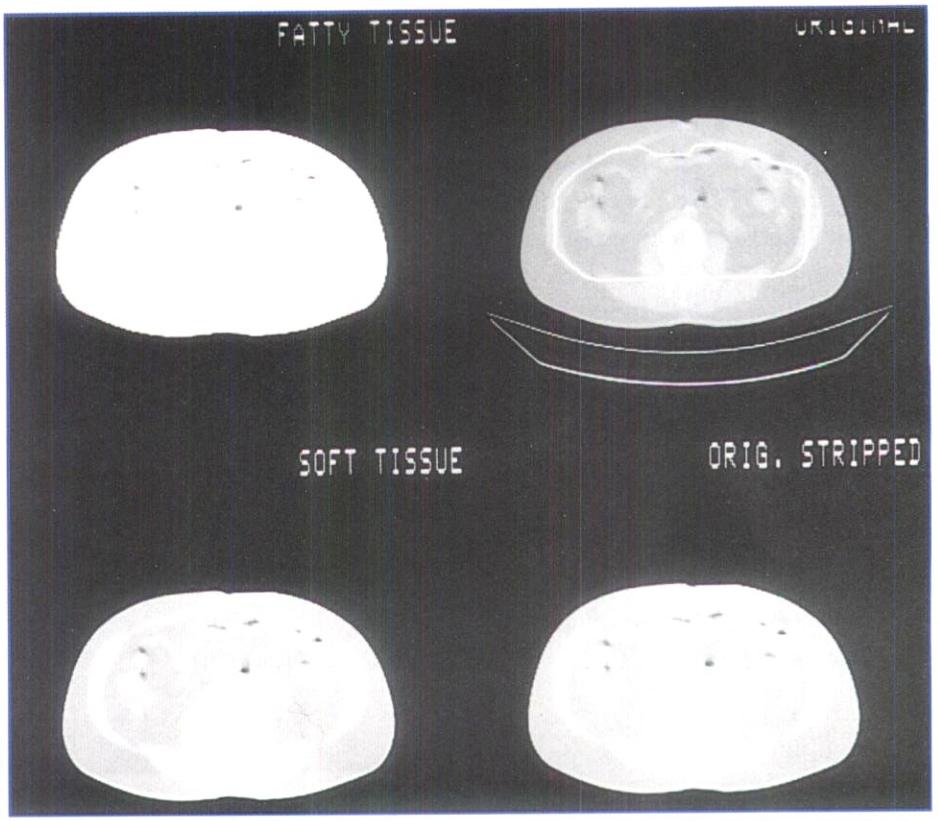
COMPUTERIZED TOMOGRAPHY

Computerized tomography (CT) scanning is the most powerful imaging technique for measuring body fat in living subjects. The method relies on the clear differences in X-ray attenuation exhibited by bone, adipose tissue and fat-free tissue. By computer processing, the information on X-ray attenuation can be represented as a cross-sectional image.

CT scans can clearly distinguish adipose tissue from other tissues and can differentiate between subcutaneous fat and visceral fat in an abdominal cross section, as illustrated in Figure 15. A single CT scan is able to measure the total intra-abdominal fat tissue area (in cm^2) and by means of multiple CT scans and integration, the total intra-abdominal fat volume (in cm^3) can be deduced. However, the tissue areas of a single abdominal cross section are highly predictive of the overall volume of abdominal fat.

Figure 16 shows an abdominal CT scan obtained from a non-overweight subject. Note that the areas corresponding to subcutaneous adipose tissue and intra-abdominal adipose tissue are minimal.

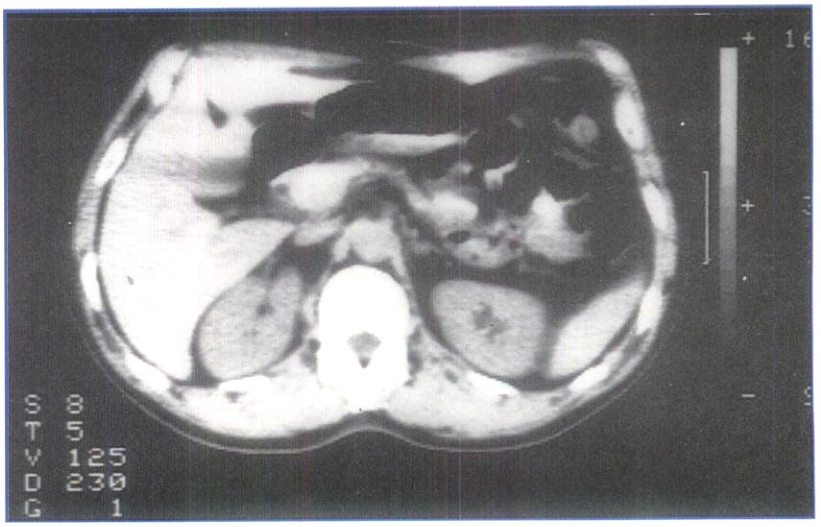
IDENTIFICATION OF VISCERAL AND SUBCUTANEOUS FAT BY CT SCAN



Dr T Weits

Figure 15: Top left: view of total fat area (shown in white by fat tissue highlighting technique); bottom left: view of soft tissue area (shown in white by soft tissue highlighting technique); top right: outline of the abdominal cavity, which separates the intra-abdominal from the subcutaneous fat; bottom right: stripped image from which the total tissue area is calculated. The distinction between intra-abdominal and subcutaneous fat areas is made by manually outlining the abdominal cavity using a joystick cursor. From Weits et al.[14]

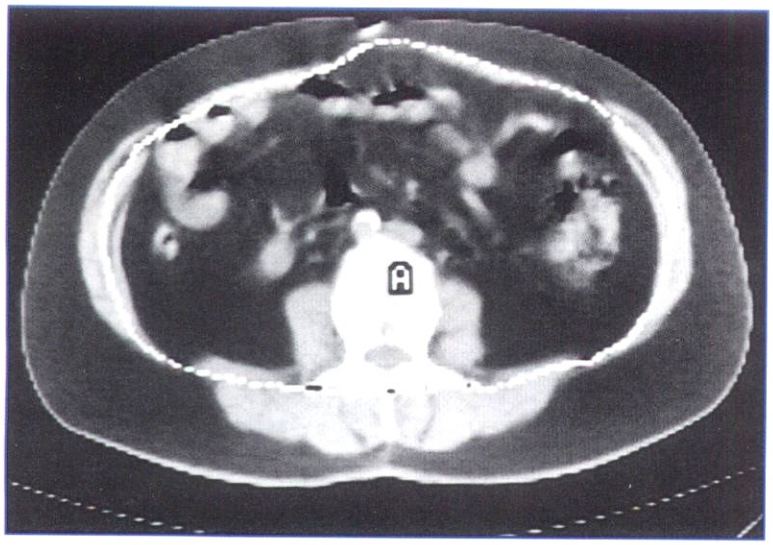
CT SCAN OF ABDOMEN OF NORMAL SUBJECT



The National Medical Slide Bank

Figure 16

CT SCAN OF ABDOMEN OF OVERWEIGHT SUBJECT WITH ABDOMINAL VISCERAL FAT



Dr T Weits

Figure 17

CT SCAN OF ABDOMEN OF OVERWEIGHT SUBJECT WITH ABDOMINAL SUBCUTANEOUS FAT

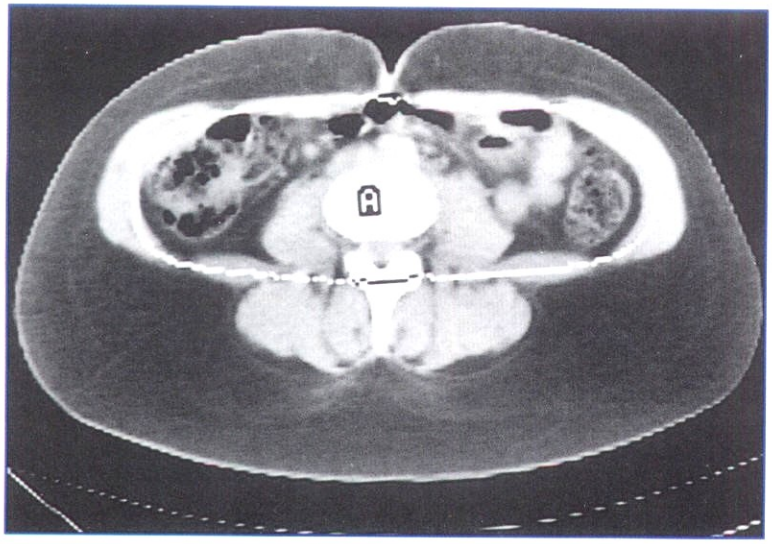


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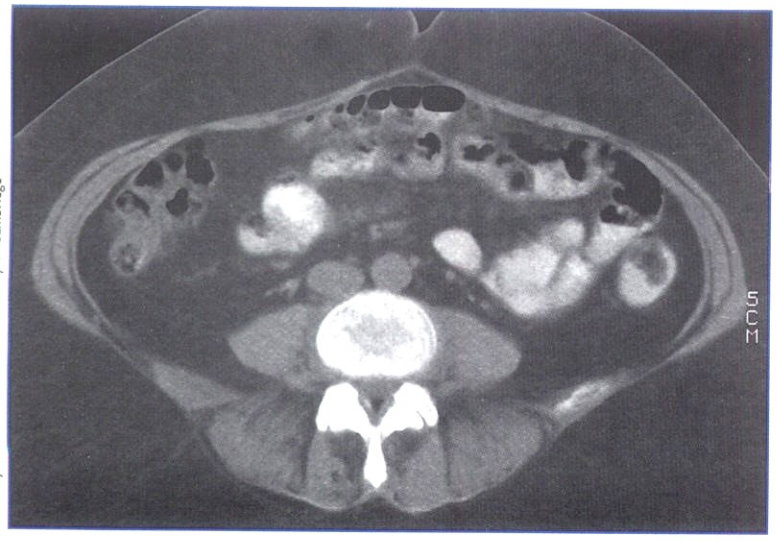
Figure 18

CT SCAN OF ABDOMEN OF OVERWEIGHT SUBJECT WITH GLUTEOFEMORAL SUBCUTANEOUS FAT



Courtesy of Professor A Dixon, University of Cambridge

Figure 19

The CT scan confirms the assessment of the ratio of abdominal to gluteofemoral fat already approximated by the WHR value. For example, the difference in distribution of adipose tissue can clearly be seen in the abdominal CT scan obtained from an overweight subject with a predominance of intra-abdominal (visceral) fat (Figure 17) and one in which the abdominal fat is mainly subcutaneous (Figure 18). Figure 19 shows a CT scan, obtained at the femoral level, from an overweight patient with gluteofemoral subcutaneous fat.

14. Weits, T., van der Beek, E.J., Wedel, M. and Ter Haar Romeny, B.M. *Int. J. Obes.*, 1988; *12:* 217–225.

MAGNETIC RESONANCE IMAGING

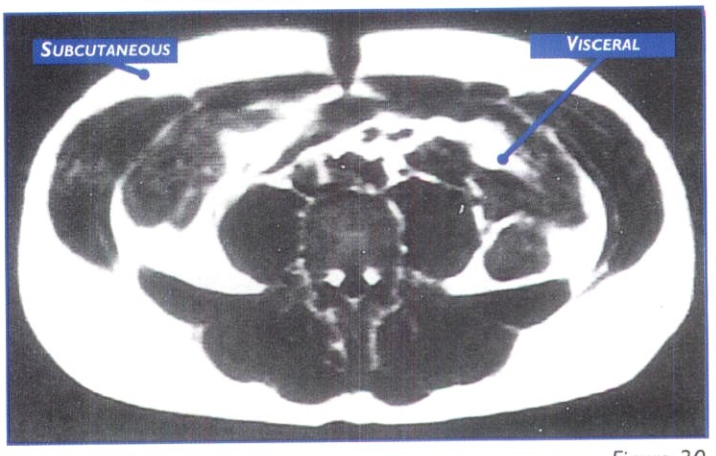
Magnetic resonance imaging (MRI) is an additional imaging technique that allows separate measurement of the different types of abdominal fat.

The technique is based upon the interaction between the nuclei of hydrogen atoms (protons), which are abundant in all biological tissues, and the magnetic fields generated and controlled by the MRI equipment. During the MRI procedure, the magnetic moments of the protons are aligned in a known direction by applying a strong magnetic field, and a pulsed radio-frequency field is applied to the body tissue, causing a fraction of the protons to absorb energy. When the radio-frequency field is turned off, the protons gradually release the energy that they have absorbed in the form of a radio-frequency signal, and this is used to develop the MRI image.

To give enhanced differentiation between skeletal muscle and adipose tissue, the specific proton densities and relaxation times (the rates at which protons release the absorbed energy) of the various tissue types can be exploited. The cross-sectional magnetic resonance images are derived in a similar manner to that for CT scans. MRI has the advantage of being safer than CT scanning, as it does not depend on the use of ionizing radiation. Thus, repeated measurements by MRI, which can be used to assess the volume of fat, do not represent a health risk for the subject.

Distinct contrasts between adipose tissue and lean tissue can be seen in MRI scans. Figure 20 illustrates an example of an abdominal MRI scan obtained at the L_4–L_5 level, in which the subcutaneous and visceral fat is clearly distinguishable from lean tissue structures. MRI scans obtained from overweight subjects with upper body fat distribution in which the abdominal fat is primarily visceral or subcutaneous are shown in Figures 21 and 22, respectively.

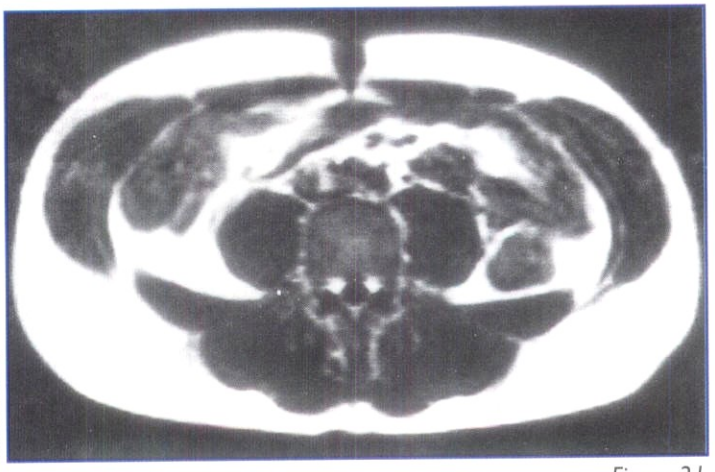
***MRI* SCAN SHOWING DISTINCTION BETWEEN VISCERAL AND SUBCUTANEOUS FAT**



Dr J Seidell

Figure 20

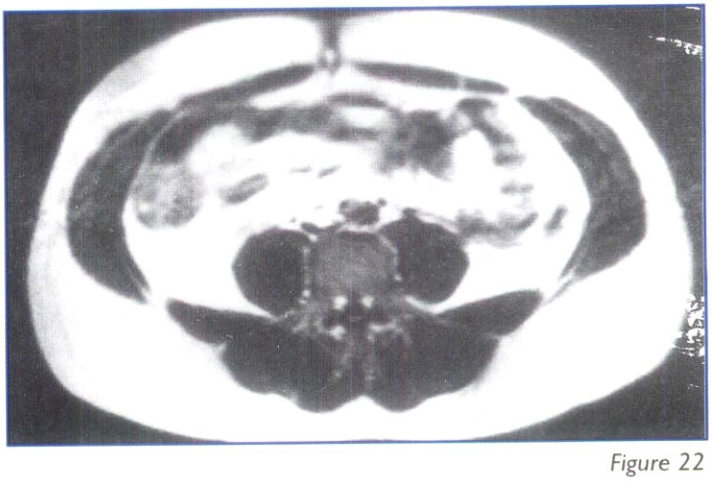
***MRI* SCAN OF ABDOMEN OF OVERWEIGHT SUBJECT WITH ABDOMINAL VISCERAL FAT**



Rianne de Leenen

Figure 21

***MRI* SCAN OF ABDOMEN OF OVERWEIGHT SUBJECT WITH SUBCUTANEOUS FAT**



Rianne de Leenen

Figure 22

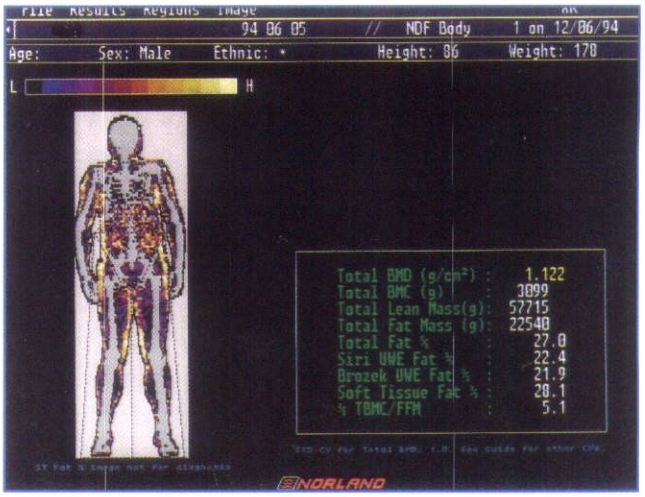
DUAL ENERGY X-RAY ABSORPTIOMETRY

Dual energy X-ray absorptiometry (DEXA) was originally designed to measure bone mineral content, but can also be used to measure total body fat mass. DEXA measurements are made using an X-ray source which produces a beam of stable dual energy radiation. The body is scanned from head to toe, typically over a period of 10–20 minutes. The ratio of the beam attenuation at the lower energy relative to that at the higher energy level (the R value) is determined, and by comparison with a calibration line of R values of known substances, the composition of soft tissue can be estimated. Although DEXA enables quantification of local (for example abdominal) fat, distinction between visceral and subcutaneous abdominal fat is not possible. Figures 23 and 24 show DEXA images obtained from overweight subjects with upper body fat distribution and lower body fat distribution, respectively.

ULTRASOUND

Ultrasound can be used to obtain a sonographic image of the interior of the body. The ultrasound beam penetrates the body and an echo is produced when the beam is reflected at a tissue interface. Ultrasound can be used to obtain either a depth measurement or a two-dimensional image of the underlying tissues in which tissue interfaces are depicted as bright lines or areas.

DEXA IMAGE FROM OVERWEIGHT SUBJECT WITH UPPER BODY FAT DISTRIBUTION



Dr Sitbon, Centre Catalogne, Paris

Figure 23

DEXA IMAGE FROM OVERWEIGHT SUBJECT WITH LOWER BODY FAT DISTRIBUTION

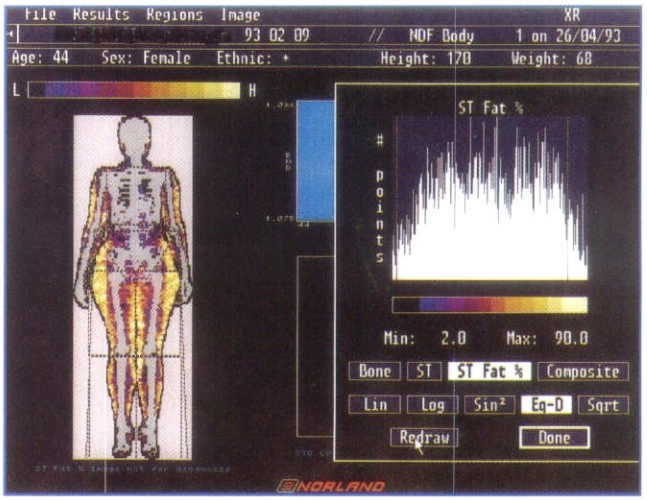


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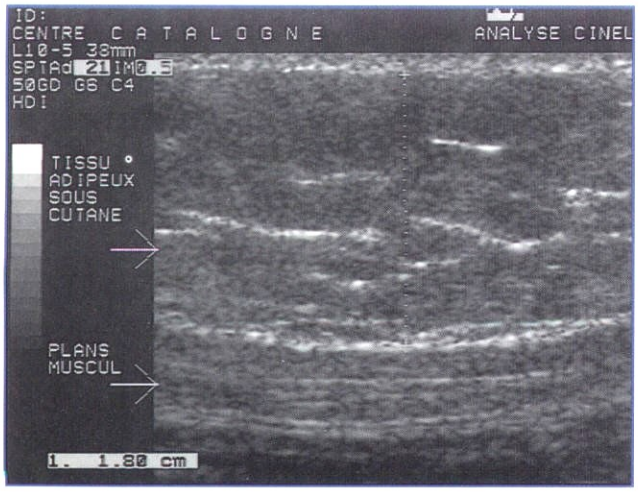
Figure 24

ULTRASOUND IMAGE OF SUBCUTANEOUS FAT



Dr Sitbon, Centre Catalogne, Paris

Figure 25

The measurement of relatively thick layers of subcutaneous fat is more conveniently performed by ultrasonography than using skinfold calipers. However, the variability of the two methods is similar. The absolute values obtained for subcutaneous fat thickness by imaging or ultrasound differ, although values for the same site obtained by these methods show a good correlation. Although the ultrasound technique has been used to measure intra-abdominal depth, the reproducibility and accuracy of this approach is poor. Thus, ultrasonography is perhaps best used for assessment of subcutaneous fat layer thickness. Figure 25 shows an ultrasound image of subcutaneous fat.

Abdominal fat distribution correlates strongly with metabolic disorders which predispose to non-insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease.[15,16]

In healthy premenopausal women,[15] increasing WHR accompanies progressive increases in steady-state plasma glucose (SSPG) (Figure 26) and steady-state plasma insulin (SSPI) levels. Moreover, increasing WHR correlates with a significant decline in the percentage increase in quadriceps glycogen synthase I activity (ΔGSI) produced by submaximal levels of insulin (Figure 26). This decline correlates with the increase in SSPG, suggesting that the impaired insulin sensitivity of skeletal muscle contributes to the overall defect in glucose disposal.

In age- and weight-matched female subjects,[15] those with upper body fat distribution exhibit a significant decrease in hepatic insulin extraction, both at baseline and during iv. or oral glucose stimulation, relative to lean subjects or those with lower body fat distribution. As a consequence, post-hepatic insulin delivery is progressively increased and correlates well with the degree of peripheral hyperinsulinaemia. Furthermore, the diminished hepatic insulin extraction in the upper body overweight subjects is proportional to the decline in peripheral insulin sensitivity.

RELATIONSHIP BETWEEN BODY FAT DISTRIBUTION AND METABOLIC DISORDERS

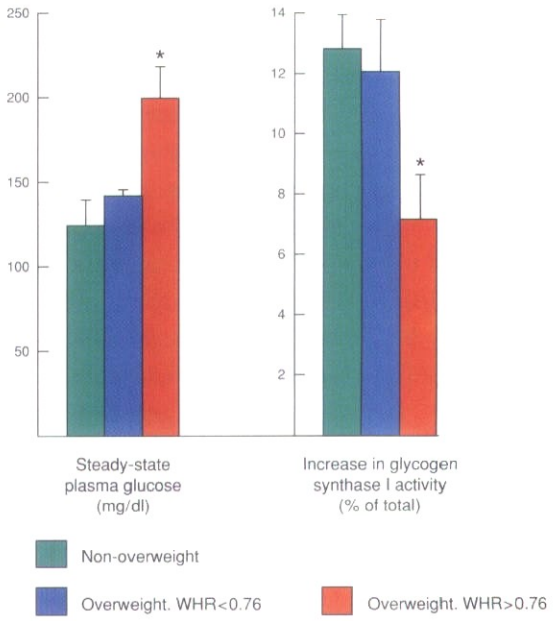


*Figure 26: * = significantly different from non-overweight, P< 0.05 or less. Adapted from Kissebah and Peiris.[15]*

CORRELATION OF UPPER BODY FAT DISTRIBUTION WITH DYSLIPIDAEMIA AND DYSLIPOPROTEINAEMIA

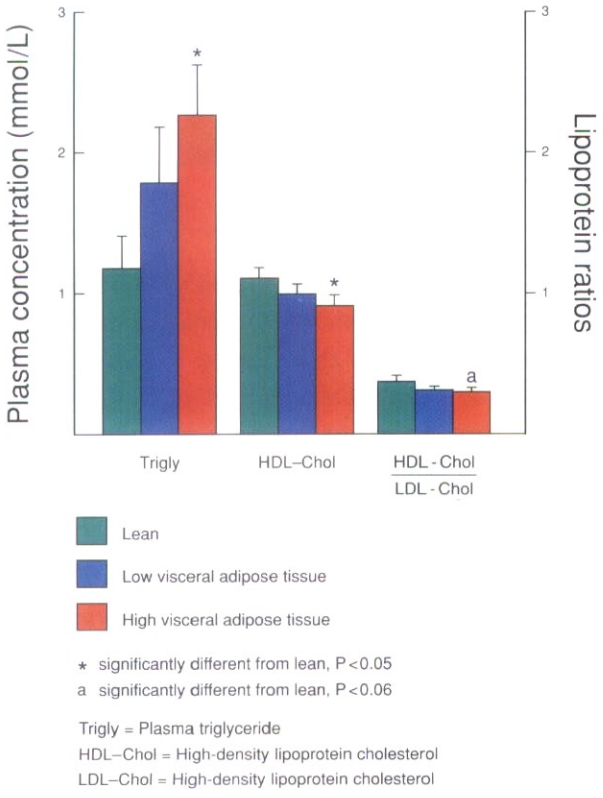


Figure 27: From Pouliot et al.[16]

Upper body fat distribution also correlates with dyslipidaemia and dyslipoproteinaemia. In overweight male subjects with high levels of visceral adipose tissue (as measured by CT scan), significantly higher fasting levels of plasma triglyceride and significantly lower plasma high-density lipoprotein (HDL) including HDL_2-cholesterol levels are observed compared with non-overweight subjects with normal levels of visceral adipose tissue (Figure 27). In this study,[16] the best morphological correlate of plasma triglyceride and HDL cholesterol levels was the ratio of visceral fat to femoral fat.

Relationship between visceral adipose tissue and predisposition to diabetes in male subjects

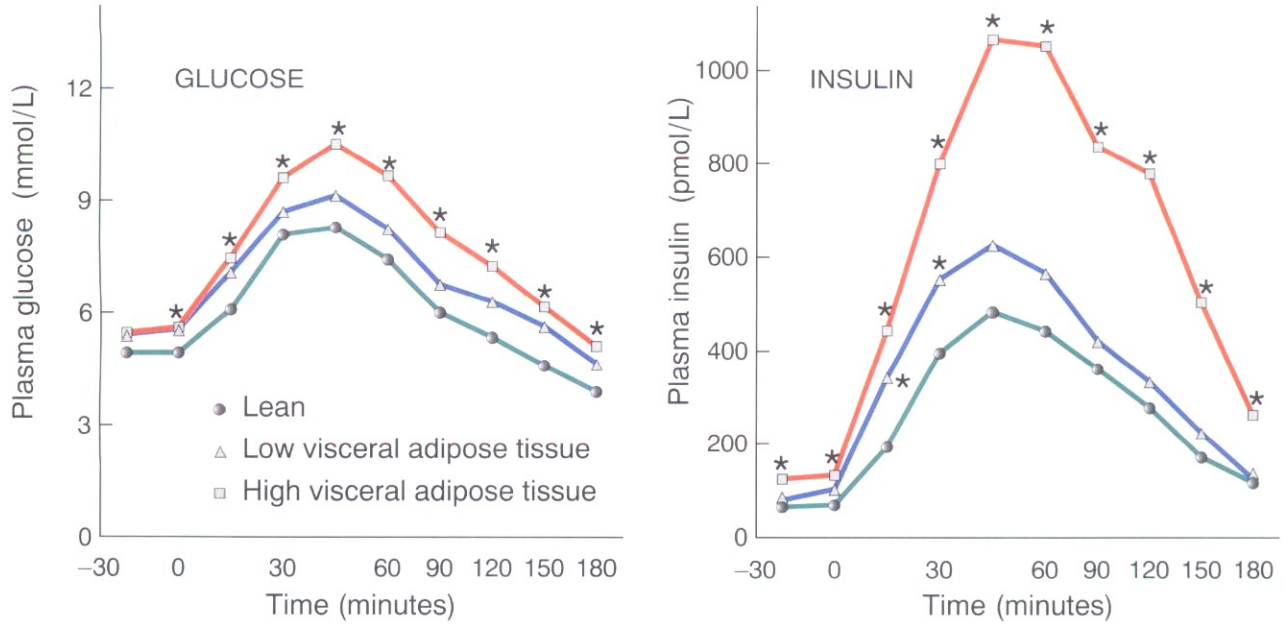


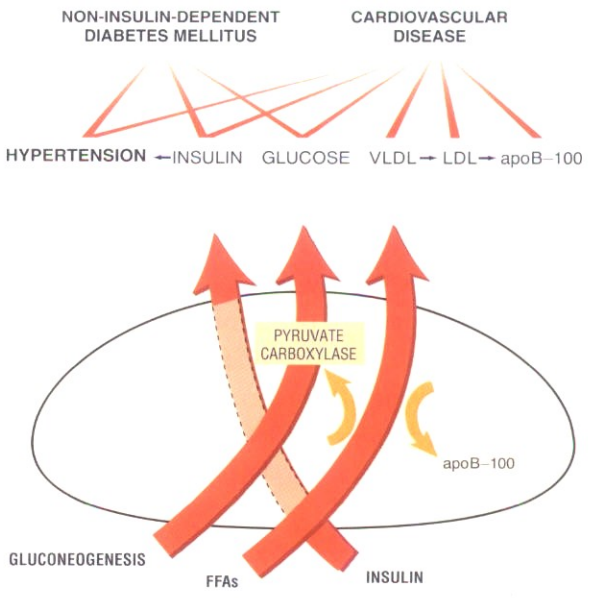
*Figure 28: Plasma glucose and insulin levels during a 75-g oral glucose tolerance test. *Significantly different from group of lean subjects. From Pouliot* et al.[16]

The adverse effects of visceral fat on glucose/insulin homeostasis are shown in Figure 28. Male subjects[16] with high levels of visceral fat show a markedly different response during an oral glucose tolerance test (OGTT), with significantly higher plasma glucose and insulin levels in the fasting state and during the OGTT.

The health risk posed by visceral fat can be understood from a consideration of the differences between abdominal visceral fat and subcutaneous fat. Visceral fat cells are characterized by a decreased sensitivity to the antilipolytic effects of insulin and increased sensitivity to the lipolytic actions of catecholamines and cortisol. As a consequence, visceral adipocytes release relatively high amounts of fatty acids.

The relationship between visceral fat and the main risk factors for cardiovascular disease and NIDDM is illustrated in Figure 29. Hepatic exposure to portal FFAs, a consequence of the lipolytic activity of portal adipose tissue, stimulates synthesis of VLDL and gluconeogenesis and inhibits hepatic insulin clearance. Amplification of these effects, as in subjects with enlarged visceral fat depots, may lead to increased concentrations of VLDL, low-density lipoprotein (LDL), apolipoprotein B-100 (apoB-100), glucose, insulin and perhaps secondarily, hypertension.[12]

Specific health complications associated with visceral fat



apoB–100 = Apolipoprotein B–100
LDL = Low-density lipoprotein
FFAs = Free fatty acids
VLDL = Very-low-density lipoprotein

Figure 29: From Björntorp.[12]

15. Kissebah, A.H. and Peiris, A.N. *Diabetes Metab. Rev.*, 1989; *5:* 83–109.

16. Pouliot, M.-C., Després, J.-P., Nadeau, A., Moorjani, S., Prud'homme, D., Lupien, P.J., Tremblay, A. and Bouchard, C. *Diabetes,* 1992; *41:* 826–834.

Body Fat Distribution and Stroke, Ischaemic Heart Disease and Death

The association between WHR and the risk of stroke, ischaemic heart disease and death from all causes has been analyzed in a 13-year prospective study of the general male population comprising 792 subjects aged 54 years at entry to the study.[10]

STROKE

Figure 30 depicts the percentage probability of stroke in relation to tertiles of BMI and WHR for the subjects in this study. For subjects within the same BMI group, the risk of stroke increased with increasing WHR, and the highest risk of stroke was observed in subjects who were in the third tertile for both BMI and WHR.

ISCHAEMIC HEART DISEASE

A similar effect was observed for risk of ischaemic heart disease (Figure 31). For this outcome the highest risk (20.8%) was observed with a high WHR, and the lowest risk (5.6%) was found in subjects with a low WHR.

MORTALITY

The trend for overall mortality was similar to that for ischaemic heart disease (Figure 32). For those with the highest WHR the risk of death was 29.2% and for those with the lowest WHR the risk of death was 5.3%.

Of a number of indicators of overweight (BMI, sum of three skinfold thickness measurements, waist or hip circumference, WHR), only WHR was significantly correlated with the occurrence of stroke and ischaemic heart disease. Furthermore, the correlation between WHR and death was also significant when BMI or the sum of three skinfold measurements was accounted for.

Correlation between WHR and percentage probability of stroke

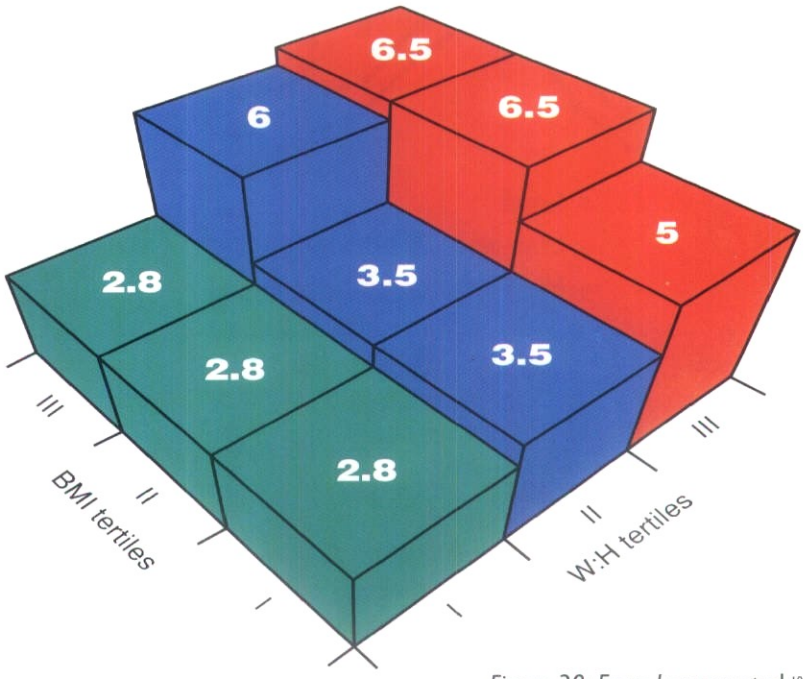


Figure 30: From Larsson et al.[10]

Correlation between WHR and percentage probability of ischaemic heart disease

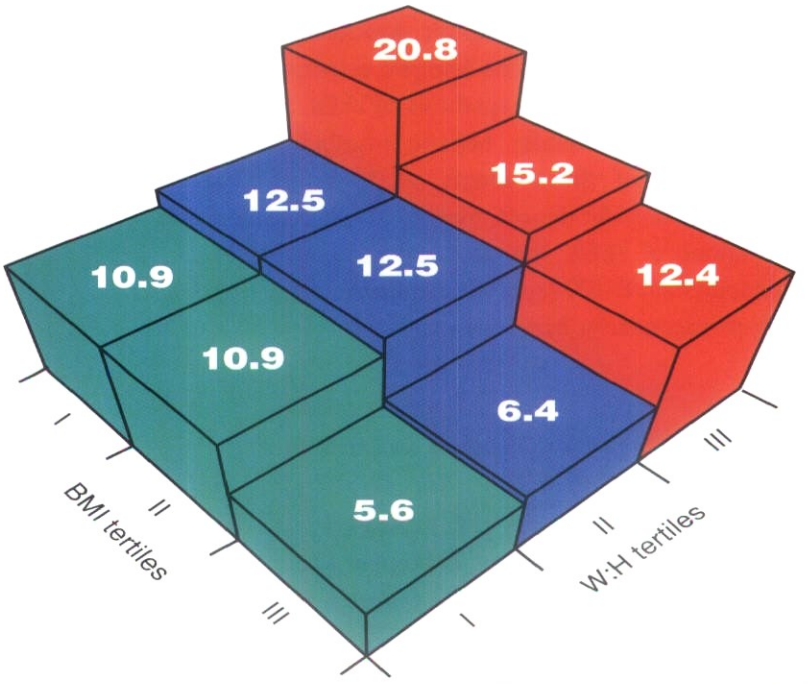


Figure 31: From Larsson et al.[10]

CORRELATION BETWEEN WHR AND PERCENTAGE PROBABILITY OF DEATH

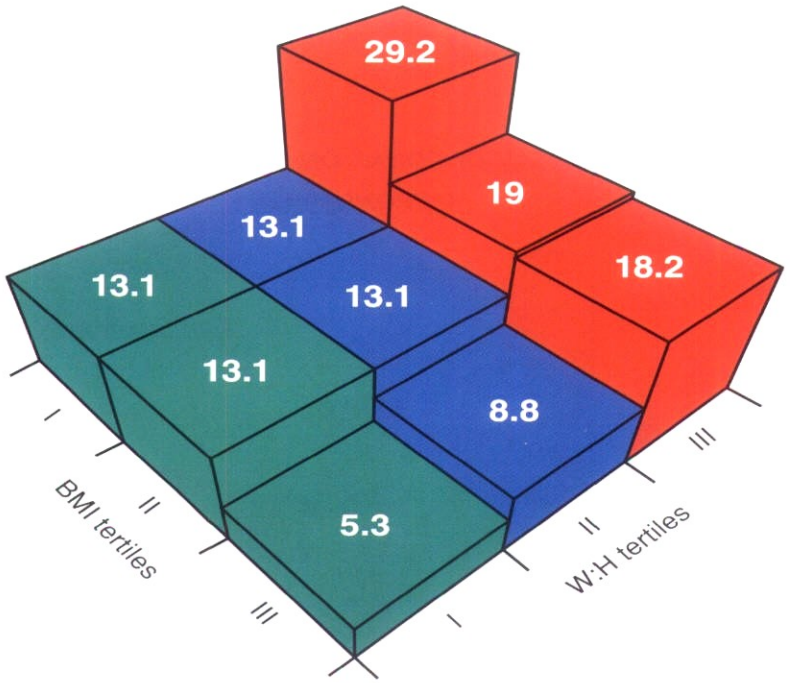


Figure 32: From Larsson et al.[10]

Figure 33 illustrates the percentage distribution of WHR values in a sample of the general population of middle aged males.[10] Approximately one-third of this population have a WHR value of 0.95 or greater, placing them at increased risk of health complications, regardless of their body mass index. Figure 34 shows the distribution of waist/hip circumference ratios in a group of 50-year-old female subjects.[11] The normal distribution is skewed to the left relative to the distribution seen in male subjects of a similar age, with the most common WHR value being in the range 0.70 – 0.74.

DISTRIBUTION OF WHR VALUES IN A POPULATION OF 54-YEAR-OLD MALE SUBJECTS

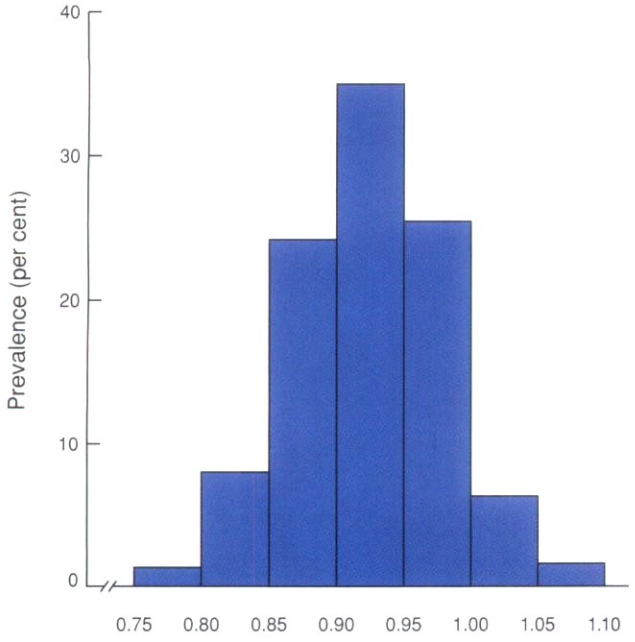


Figure 33: From Larsson et al.[10]

DISTRIBUTION OF WHR VALUES IN A POPULATION OF 54-YEAR-OLD FEMALE SUBJECTS

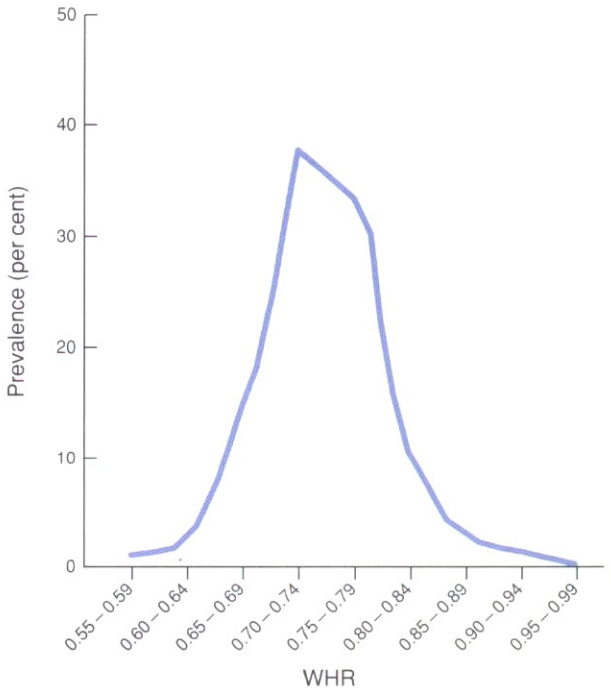


Figure 34: From Lapidus et al.[11]

A growing realization of the importance of abdominal visceral fat in the pathophysiology of overweight has led to interest in the effect of Adifax on fat distribution. This effect is truly relevant to the management of overweight patients, and reinforces the therapeutic importance of Adifax in the treatment of overweight.

Adifax reduces fat and carbohydrate consumption while maintaining the intake of essential foodstuffs such as protein (Figure 35).[17] The efficacy of Adifax in restoring healthier eating habits has been demonstrated in various clinical situations: carbohydrate snacking, overeating during large meals, and macronutrient imbalance.

With Adifax, dietary compliance is improved, and the chance of achieving a given weight loss target is doubled.

THE EFFECT OF ADIFAX ON CONSUMPTION OF MACRONUTRIENTS

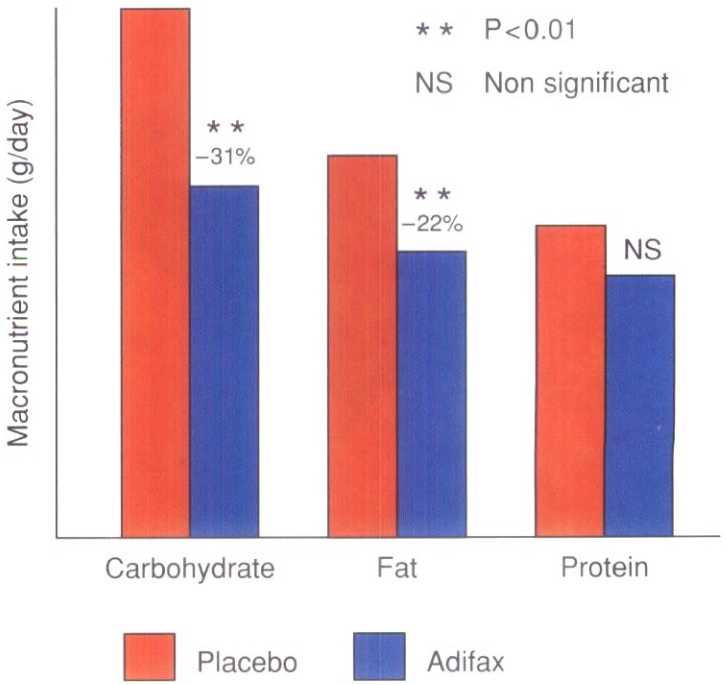


Figure 35

1. A PREDOMINANT EFFECT ON ABDOMINAL FAT

An important study[18] was undertaken to determine the site of weight loss with Adifax. MRI, a state of the art technique, allows serial assessment of abdominal visceral and subcutaneous fat (Figures 36 and 37). After 3 months' treatment with Adifax, the loss of abdominal visceral fat was impressive.

MRI TRANSVERSE SECTION AT L_3-L_4 LEVEL OF OVERWEIGHT SUBJECT BEFORE TREATMENT WITH ADIFAX

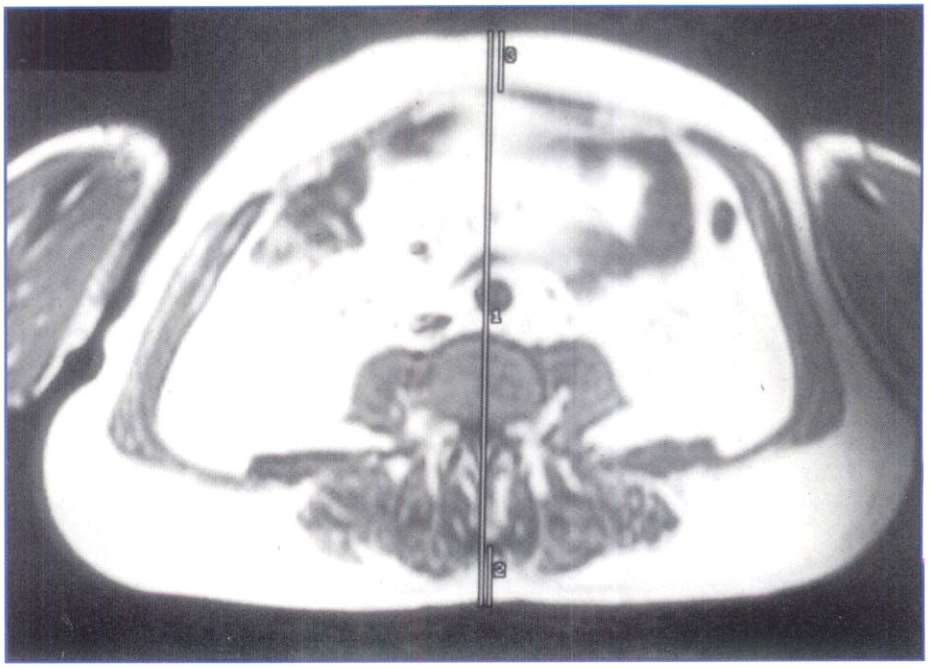


Figure 36

MRI TRANSVERSE SECTION AT L_3-L_4 LEVEL OF OVERWEIGHT SUBJECT AFTER 3 MONTHS' TREATMENT WITH ADIFAX

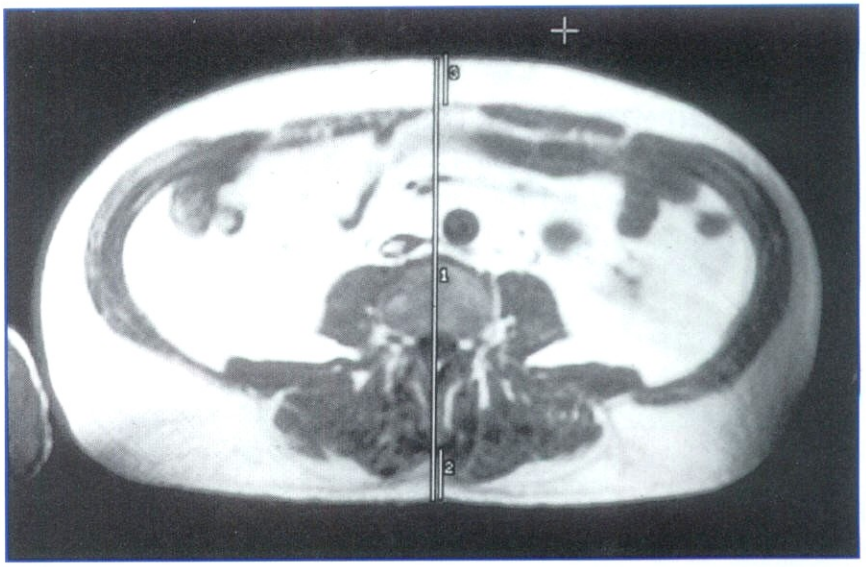


Figure 37

II. ADIFAX AND WAIST TO HIP RATIO

The waist to hip ratio (WHR) depends on both the visceral and subcutaneous components of abdominal fat. In the same study,[18] based on MRI measures, the WHR was significantly reduced at the end of treatment with Adifax 15 mg twice daily (Figure 38).

This reduction is very relevant as WHR is directly related to morbidity independently of body weight and BMI.

III. ADIFAX SELECTIVELY REDUCES VISCERAL FAT

Visceral fat alone, and not subcutaneous fat appears to be responsible for the disturbance of glucose and lipid metabolism in overweight. A precise measurement of visceral fat[18] showed a 28% reduction after Adifax treatment (Figure 39).

IV. ADIFAX AND ABDOMINAL OVERWEIGHT

Adifax's effect on visceral fat may explain its particular efficacy in abdominal (android) overweight. This feature of Adifax's action was highlighted in a study of Adifax versus placebo in a population of obese women.[19] Women with abdominal (android) obesity lost significantly more weight than those with the gluteofemoral (gynoid) pattern (Figure 40).

THE EFFECT OF ADIFAX ON WHR[18]

M_0 at start of treatment with Adifax.
WHR = 0.95 ±0.04

M_3 after 3 months' treatment with Adifax.
WHR = 0.89 ±0.03

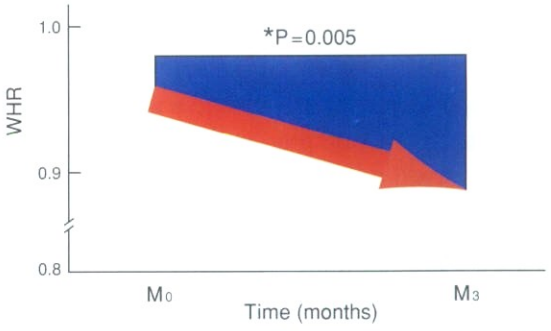


Figure 38

TREATMENT WITH ADIFAX REDUCES ABDOMINAL VISCERAL FAT[18]

M_0 at start of treatment.
Visceral fat = 4876 ±2129 mm²

M_3 after 3 months' treatment with Adifax.
Visceral fat = 3537±1770 mm²

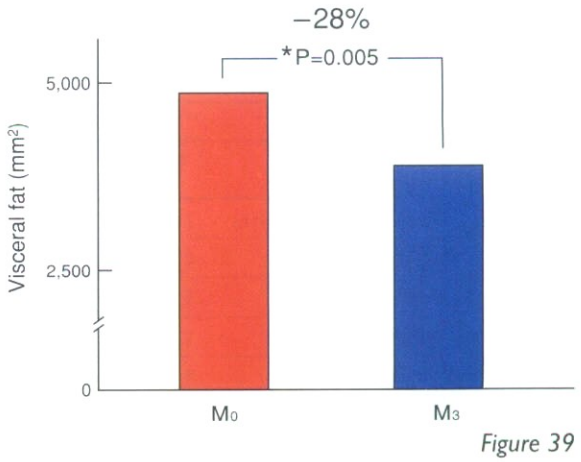


Figure 39

Treatment with Adifax enhances weight loss in overweight women with upper body fat distribution[19]

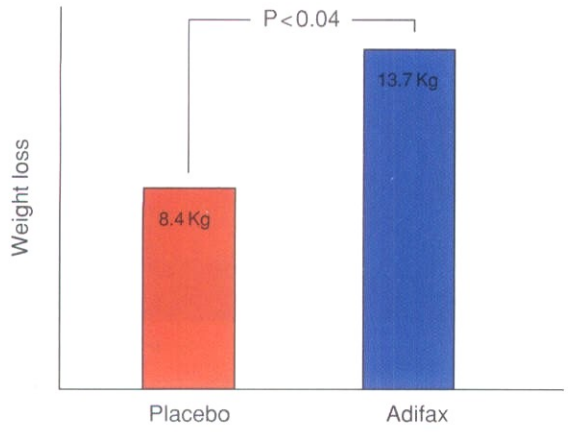


Figure 40

Reduction in plasma glucose and insulin levels after treatment with Adifax[20]

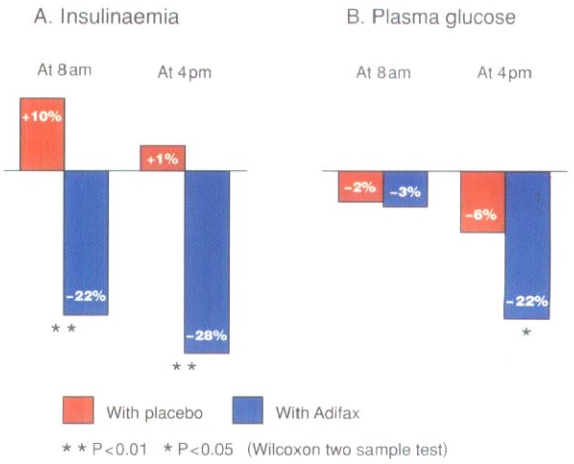


Figure 41

V. ADIFAX AND RISK FACTORS RELATED TO ABDOMINAL OVERWEIGHT

In a placebo-controlled study,[20] Ditschuneit *et al* showed significant reduction in plasma glucose and insulin in Adifax-treated subjects (Figure 41). A recent study[21] has also shown an improvement in lipid profile, with reduced total and LDL cholesterol, and triglycerides (Figure 42). A large multicenter study[22] went on to show significant reductions in blood pressure in overweight hypertensive subjects.

By targeting visceral fat, Adifax specifically decreases the fat that is hazardous to health. Adifax, therefore, improves the metabolic profile which may contribute to a better prognosis for overweight. Adifax is efficient in all overweight patients. The prescription of Adifax in patients with abdominal fat distribution is even more relevant.

17. Brzezinski, A.A., Wurtman, J., Wurtman, R., Gleason, R., Greenfield, J. and Nader, T. *Obstet. Gynecol.,* 1990; *76(2):* 296–301.

18. Marks, S.J., Moore, N.R., Hockaday, T.D.R. and Clark, M. *Int. J. Obes. 1994; 18 (Suppl 2): 59.*

19. Van Gaal, L., Vansant, G., Vandevoorde, K., Biasi, B. and De Leeuw, I. *Int. J. Obes.,* 1989; *13 (Suppl 1):* 141.

20. Ditschuneit, H.H., Flechtner-Mors, M., Dolderer, M., Fulda, U. and Ditschuneit, H. *Horm. Metab. Res.,* 1993; *25:* 573–578.

21. Bremer, J.M., Scott, R.S. and Lintott, C.J. *Int. J. Obes.,* 1994; *18:* 199–205.

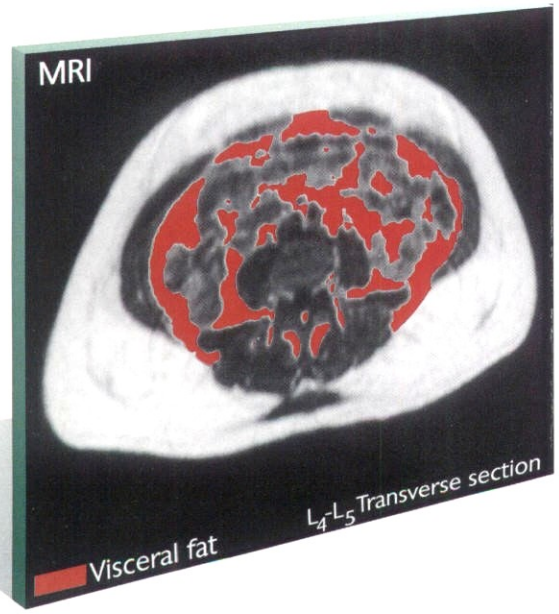
22. Crepaldi, G., Enzi, G., *et al. Int. J. Obes.,* 1992; *16 (Suppl 1):* 67.

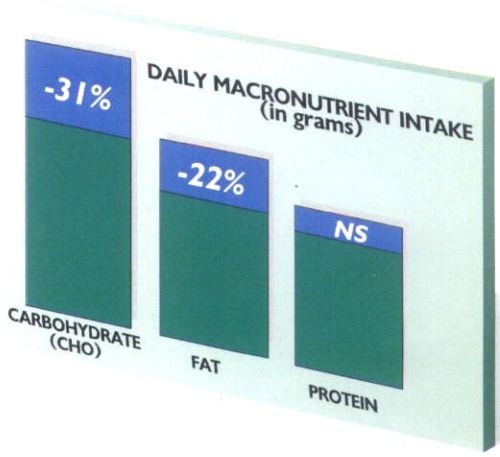
Effect of Adifax on cardiovascular risk factors[21]

	PLACEBO			ADIFAX		
	WEEK 0	WEEK 12	0 TO 12 % CHANGE	WEEK 0	WEEK 12	0 TO 12 % CHANGE
Cholesterol (mmol/L)	7.0 ±0.3	7.1 ±0.3	+1%	7.7 ±0.4	6.7 ±0.4	–13%***
LDL cholesterol	4.8 ±0.3	4.5 ±0.3	–6%	5.4 ±0.3	4.6 ±0.3	–15%***
HDL cholesterol	1.1 ±0.1	1.1 ±0.1	+2%	1.1 ±0.1	1.2 ±0.1	+11%
VLDL cholesterol	1.1 ±0.2	1.4 ±0.3	+26%	1.1 ±0.3	0.8 ±0.2	–32%***
Triglyceride	2.9 ±0.3	2.7 ±0.5	+17%	1.8 ±0.3	1.4 ±0.2	–22%*
Within group changes from 0 to 12: *** $P < 0.001$ * $P < 0.05$						

Figure 42

A major development in the management of overweight...





HEALTHIER BODY FAT DISTRIBUTION

- Specific reduction of abdominal visceral fat
- Improvement in the waist-to-hip ratio

Marks SJ. *Int J Obes.* 1994: Vol 18, Suppl 2.

HEALTHIER EATING HABITS

- Selective reduction of CHO- and fat-rich food intake
- Maintenance of essential nutrients such as protein

Brzezinski A et al. *Obstet Gynecol.* 1990; 76: 296-301.

ADIFAX®

DEXFENFLURAMINE

MORNING EVENING

promotes a healthier body weight

▼ADIFAX® dexfenfluramine

Abridged Prescribing Information

Refer to Data Sheet Before Prescribing. Indications As an adjunct to continued dietary treatment of severe obesity in patients who have not responded to an appropriate weight reducing diet alone. **Presentation** White capsules marked S 5614 each containing 15 mg dexfenfluramine hydrochloride. **Dosage and Administration** Adults: 2 capsules of 15 mg daily taken orally, one capsule in the morning and one capsule in the evening, at mealtimes. Elderly: Not recommended. Children: Contra-Indicated. Duration of treatment: This should not exceed 3 months. **Contra-Indications** Patients with glaucoma, a history of anorexia nervosa, psychiatric illness, depressive illness or history of drug or alcohol abuse. Avoid in hepatic or renal impairment. Lactation: not recommended in nursing mothers. Children. **Precautions and Warnings** Not to be used with monoamine-oxidase inhibitors (MAOIs) or centrally acting appetite suppressants. Stop MAOIs for at least two weeks before commencing treatment. The action of anti-hypertensive, anti-diabetic or sedative drugs and the hypotensive effect of tricyclic anti-depressants may be potentiated. Pregnancy - not recommended unless the benefits outweigh any possible risk (see data sheet). Depression may occur after abrupt cessation of treatment. Steady reduction of dosage over one or more weeks is recommended. Adifax is not recommended in patients with a history of epilepsy since there have been isolated reports of convulsions with dexfenfluramine. **Side Effects** Dry mouth, nausea, constipation and diarrhoea have been reported, disappearing on continuing treatment. More rarely reported are drowsiness, dizziness, urinary frequency, headache, asthenia, mood disturbance, symptoms of depression, insomnia, nervousness, confusion, blood pressure variation, faintness, diplopia, mydriasis, shivering, skin rash and conjunctivitis. Schizophreniform reactions have been reported rarely with fenfluramine (Ponderax) and there is some evidence that they may also occur with Adifax. Pulmonary hypertension has been reported rarely in patients treated with Adifax. Patients should be advised to report immediately any deterioration in exercise tolerance or increasing dyspnoea at rest. The occurrence of depression, irritability and dizziness have followed abrupt discontinuation of Adifax. **Legal Category:** POM. **Basic NHS Cost** 15 mg capsules £8.08 per pack of 60. **Product Licence Number** 5815/0003. Issued April 1990. Special reporting to CSM required. **ADIFAX®** is a registered trade mark. For further information please contact: Servier Laboratories Ltd, Fulmer Hall, Windmill Road, Fulmer, Slough, Berks, SL3 6HH. Tel (01753) 662744 Fax (01753) 663456. Date of Issue, March 1995.

95 IS 342 BA