Cardiovascular disease risk modification in abdominally obese people with type 2 diabetes

John Wilding

Article points

1. Excess visceral fat in abdominally obese type 2 diabetes patients is the underlying cause of the increased risk of CVD.
2. Waist circumference as well as BMI, should be routinely recorded as part of a patient's cardiovascular risk assessment.
3. There is a need for pharmacotherapy that targets multiple cardiovascular risk factors.

Key words

- Abdominal obesity
- Cardiovascular risk
- Visceral fat
- Waist circumference

John Wilding is a Professor of Medicine and an Honorary Consultant Physician at the Clinical Sciences Centre, University Hospital Aintree, Liverpool.

The rising prevalence of type 2 diabetes worldwide is associated with an increase in the proportion of the population with obesity (Zimmet et al, 2001; Ehtisham et al, 2004). There are an estimated 2 million people in the UK with type 2 diabetes, with up to a million more who remain undiagnosed (Diabetes UK, 2006). This review will discuss some of the evidence that supports the role that visceral fat plays in increasing cardiovascular disease (CVD) risk in abdominally obese people with type 2 diabetes.

The prevalence of type 2 diabetes worldwide is expected to more than double between the years 1995 and 2025 (Amos et al, 1997), and in the UK numbers are expected to increase by about 40% (King et al, 1998). Approximately 80–90% of people with type 2 diabetes are obese (Norris et al, 2005). A recent audit of approximately 3000 people attending a secondary care diabetes clinic has shown that glycaemic control worsens with increasing weight (Daousi et al, 2005). Obesity worsens the physiological, cardiovascular and metabolic abnormalities associated with type 2 diabetes, including hyperglycaemia, hyperlipidaemia and hypertension (Norris et al, 2005).

Excess visceral fat and elevated cardiometabolic risk

There are two main components of metabolically active adipose tissue: these are subcutaneous fat and intra-abdominal fat (often referred to as visceral fat).

The presence of excess visceral fat in abdominally obese individuals is associated with an increased risk of type 2 diabetes and CVD (Despres et al, 2001; Van Gaal et al, 2005; Eckel et al, 2005). Visceral fat can be measured accurately by using a computed tomography scan, but a simple measurement of the waist circumference is a good surrogate measure. Examples of risk factors for type 2 diabetes and CVD that are associated with increased visceral fat include raised concentrations of fasting plasma glucose and triglycerides, reduced levels of HDL cholesterol and high blood pressure. Collectively, these risk factors, in addition to other classical risk factors such as high LDL cholesterol, contribute to an individual's 'cardiometabolic risk profile'. An individual who is abdominally obese is thought to be at high cardiometabolic risk and is more likely to develop type 2 diabetes and CVD (Eckel

Page points

1. Obesity in people with type 2 diabetes worsens metabolic and physiological abnormalities and also there are higher mortality rates for obese individuals with diabetes than those without.
2. Increased visceral fat is associated with high levels of free fatty acids in the blood.
3. Visceral obesity is associated with impaired glucose uptake in response to insulin in the liver.
4. There is evidence suggesting that surgical procedures, such as liposuction, do not alter the insulin sensitivity of muscle, liver or adipose tissue.

et al, 2005). A person with type 2 diabetes who is also abdominally obese is at a greater risk of developing CVD (Stumvoll et al, 2005; Maggio and Pi-Sunyer, 1997).

A recent Cochrane review has acknowledged that obesity worsens the metabolic and physiological abnormalities associated with type 2 diabetes (Norris et al, 2005). In addition, obese individuals with diabetes have higher mortality rates than those who are not obese (Maggio and Pi-Sunyer, 1997). In abdominally obese people with type 2 diabetes, evidence suggests that it is the excess visceral fat that is associated with poor metabolic control, atherogenic blood lipid levels and cardiovascular complications, even in the absence of overall obesity (Maggio and Pi-Sunyer, 1997). Evidence also suggests that insulin resistance associated with excess visceral fat is another possible factor contributing to the increased health risks of abdominal obesity (Maggio and Pi-Sunyer, 1997).

Link between excess visceral fat, insulin resistance and increased cardiometabolic risk

Several hypotheses have been proposed to explain the link between increased visceral fat and insulin resistance; these include high levels of free fatty acids (FFAs) and the production of proteins from fat that impair insulin action (Wajchenberg, 2000; Fasshauer and Paschke, 2003; Ritchie et al, 2004). It is likely that both contribute to the development of insulin resistance.

In brief, increased visceral fat is associated with high levels of FFAs in the blood, particularly in the portal circulation after a meal. This results in an increase in glucose production in the liver and reduced insulin clearance. High FFA levels in the systemic circulation also compete for glucose uptake and metabolism in skeletal muscle, so that more insulin is needed to enable glucose uptake. Protein molecules secreted by adipose tissue, known as adipokines, also play a pivotal role in insulin resistance by directly influencing insulin action (Fasshauer and Paschke, 2003). These include tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), leptin and adiponectin. The levels of all of these adipokines, apart from adiponectin, are raised with increasing visceral fat accumulation (Wajchenberg, 2000; Ritchie et al, 2004). Adiponectin is suggested to have anti-inflammatory and anti-atherogenic properties (Ritchie et al, 2004); therefore, reduced levels of this adipokine, observed in abdominal obesity, may further contribute to its attendant cardiometabolic risk.

Thus visceral obesity is associated with impaired glucose uptake in response to insulin in the liver and muscle and decreased clearance of insulin from the circulation, as a result of increased FFA levels, increased pro-inflammatory cytokines and decreased adiponectin. In people without diabetes this is compensated for by increased insulin secretion, but diabetes develops when insulin secretion is unable to keep up with the increased demand in the face of insulin resistance.

There is also supporting evidence from studies using surgical procedures for the contributory role of visceral fat to the development of CVD. Thorne et al (2002) reported that the improvements in oral glucose tolerance, insulin sensitivity and fasting plasma glucose and insulin in omentectomised people (i.e. those who had visceral fat removed surgically) were 2–3 times greater than in the control subjects ($P = 0.009–0.04$). Klein et al (2004), on the other hand, reported that liposuction, which removed subcutaneous fat, did not significantly alter the insulin sensitivity of muscle, liver or adipose tissue. In addition, it did not have a significant effect on plasma concentrations of C-reactive protein, IL-6, TNF-α, or adiponectin. Furthermore, it had no significant effect on other risk factors for coronary heart disease (such as blood pressure, plasma glucose, and insulin and lipid levels) in abdominally obese women with normal glucose tolerance (n = 8) or with type 2 diabetes (n = 7).

A recent multinational study reporting a strong relationship between waist-to-hip ratio (WHR; as a measure of abdominal obesity)

Page points

1. Recent evidence suggests there is a relationship between waist-to-hip ration and waist circumference with risk of myocardial infarction.
2. Waist circumference measurement correlates better with the accumulation of visceral fat than WHR.
3. Waist circumference measurements are associated with insulin sensitivity and can be used to predict the likelihood of insulin resistance in individuals.
4. Weight-loss is an important treatment for those patients with diabetes who are overweight or abdominally obese.

and waist circumference with myocardial infarction risk, is also supportive of the adverse role that visceral fat has on the risk of developing CVD (Yusuf et al, 2005).

There have been many attempts to use a combination of risk factors to estimate the risk of CVD in people, however, in the author's opinion these have limited accuracy. Those based on the Framingham study tend to underestimate the risk of developing CVD for those with diabetes. The UKPDS risk engine is diabetes specific, but has not been validated in a non-trial population. High waist circumference has been advocated to be a good indicator of cardiometabolic risk (Yusuf et al, 2005; Wahrenberg et al, 2005; Wang et al, 2005; Waine, 2006) and thus may be a useful surrogate marker of CVD risk in abdominally obese people with type 2 diabetes in clinical practice. The recently published Joint British Societies' guidelines on the prevention of CVD in clinical practice (JBS2) have included waist circumference cut-off points for abdominal obesity in addition to BMI specifications for general obesity (British Cardiac Society et al, 2005).

Waist circumference as a good indicator of cardiovascular risk

In an early study of 81 men and 70 women, waist circumference was found to correlate better with visceral fat accumulation, as measured by computed tomography, than with the then commonly used WHR (Pouliot et al, 1994). Waist circumference also appeared more closely related to metabolic variables than WHR, especially among women. This led the authors to suggest that waist circumference should be used as an index of visceral fat deposition and in the assessment of CV risk.

It has also previously been recommended that waist circumference be used in routine clinical practice in the identification of abdominally obese people (Despres et al, 2001). More recently, the International Diabetes Federation (IDF) has suggested waist circumference cut-off points of ≥94 cm for Europid men and ≥80 cm for Europid women in the identification of people with metabolic syndrome, of which abdominal obesity is a prerequisite (Alberti et al, 2005).

Recent studies have also shown waist circumference measurements to be associated with insulin sensitivity (Wahrenberg et al, 2005). Waist circumference measurement has been advocated to be a useful tool to identify those at greatest risk of developing insulin resistance, i.e. those who would benefit most from interventions to change lifestyle and body weight (Wahrenberg et al, 2005). A waist circumference of <100 cm makes insulin resistance unlikely in men and women (Wahrenberg et al, 2005). Moreover, waist circumference (as a measure of abdominal obesity) has also been found to be associated with an increased risk of developing type 2 diabetes (Wang et al, 2005). Therefore, waist circumference may serve as a good indicator of cardiovascular risk, and thus may be important, along with BMI, as part of an individual's risk assessment in a clinical setting.

Discussion with patients regarding the importance of waist circumference may be useful during their clinical reviews. This would reinforce the essential message that lifestyle changes, such as regular exercise and dietary modifications are an essential part of managing overall cardiometabolic risk, along with appropriate pharmacotherapy. It is particularly important that those with a BMI within the high-optimal/just overweight ranges (24–27 kg/m^2 respectively) understand the importance of measuring waist circumference. Otherwise they may believe that they are at low risk of CVD and so may be less inclined to maintain their lifestyle modifications and treatment regimens.

It is, of course, important to praise patients who have succeeded in losing weight and reducing their waist circumference. The measurements of waist circumference and weight made at each review can be used as an incentive to maintain treatment regimens, as patients will have a record of the progress they are making. Equally, those who have maintained their treatment regimen and

lifestyle changes but have not lost weight should also be encouraged. Benefits of regular exercise and dietary modifications (even without any actual weight loss) include improved cardiovascular function and insulin resistance. These benefits should be explained clearly so that patients do not feel as if they have 'failed' or that their difficult lifestyle changes are having no effect.

Recommended method of measuring waist circumference

The World Heart Federation has made recommendations on how waist circumference measurements should be taken (*Figure 1*). If this method is adopted by all healthcare professionals when assessing cardiometabolic risk, any variations within and between different general practices can be negated, thus allowing fair data comparisons to be made.

Cardiometabolic risk reduction in people with type 2 diabetes and abdominal obesity

Epidemiological studies have suggested that weight loss is an important treatment target in the high proportion of people with type 2 diabetes who are also overweight or abdominally obese (Williamson et al, 2000; Lean et al, 1990). These individuals are likely to have a higher cardiometabolic risk profile than their leaner counterparts without diabetes. In people with type 2 diabetes, excess visceral fat, even in the absence of general obesity, has been associated with poor glycaemic control, atherogenic blood lipid levels and cardiovascular complications (including peripheral vascular disease, coronary ischaemic heart disease and hypertension; Van Gaal, 1988). Weight loss of between 5% and 10% is associated with an approximate reduction in visceral fat content of 30% (Despres et al, 2005).

Although studies have shown that most of the early reduction in fasting glucose in dieting individuals is due to energy restriction rather than weight loss per se (Henry et al, 1986; Kelley et al, 1993), in the longer term, as weight loss is maintained, there is a reduction in HbA_{1c}, suggesting a continued improvement in glycaemic control (Maggio and Pi-Sunyer, 1997). Although hyperglycaemia was shown to be significantly improved in those who achieved greater than 5% weight loss, the general consensus is that a 10% weight loss is probably required to achieve significant reduction of HbA_{1c} in people with type 2 diabetes (Wing et al, 1987). Weight loss is also associated with an improvement in insulin resistance (Maggio and Pi-Sunyer, 1997) and insulin sensitivity (Pi-Sunyer, 2000), and intentional weight loss is linked with reduced mortality in people with diabetes (Williamson et al, 2000). In addition, weight loss improves lipid profiles and improves blood pressure (Maggio and Pi-Sunyer, 1997) thus supporting the recommendation that people with type 2 diabetes and abdominal obesity should attempt to lose weight. However, the weight loss induced by diet and lifestyle modifications alone is difficult to sustain over a long period of time (Norris et al, 2005).

Therefore in certain cases, pharmacological intervention, along with lifestyle and dietary advice, may be necessary in order to improve a patient's cardiometabolic risk profile. Historically, pharmacological agents have primarily targeted individual cardiometabolic risk factors. There are a number of therapeutic options available in the management of people with type 2 diabetes, including metformin, glitazones, sulphonylureas and insulin, as reflected by NICE

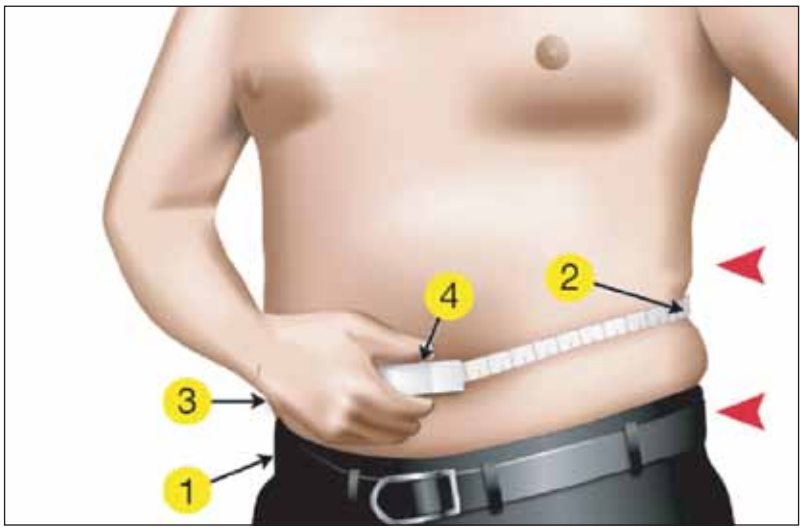

Figure 1. Step-by-step recommendations for measuring waist circumference.
(Diagram reproduced with kind permission from the World Heart Federation.)
1) Place a tape measure around the bare abdomen just above the hip bone.
2) Position the tape measure parallel to the floor, midway between the top of the iliac crest and the lower rib margin on each side.
3) Ensure the tape measure is snug, but not compressed against the skin.
4) As the individual relaxes and exhales, the waist measurement can be taken.

guidelines (NICE, 2002).

However, with the exception of metformin, weight gain is a well recognised side effect of many of the current anti-diabetic therapies (Purnell and Weyer, 2003), which can prove challenging when managing the broader cardiometabolic risk profile of an individual, and these agents do not treat other cardiometabolic risk factors such as dyslipidaemia. Many abdominally obese people, with or without diabetes, also receive statins and anti-hypertensives to treat dyslipidaemia and raised blood pressure. Statins used in those with diabetes have been shown to reduce CVD by approximately 30% (Colhoun et al, 2005). Nevertheless, statins do not treat other cardiometabolic risk factors such as hyperglycaemia or abdominal obesity and the majority of people with type 2 diabetes die of CVD.

The weight loss drugs orlistat and sibutramine have been shown to be at least modestly effective at promoting weight loss and are of benefit to some people with type 2 diabetes (Hollander et al, 1998; McNulty et al, 2003). A Cochrane review found that, compared with placebo, those treated with orlistat lost, on average 2.7 kg more weight and those treated with sibutramine experienced 4.3 kg greater weight loss. The percentage of people achieving 10% or greater weight loss was 12% higher with orlistat and 15% higher with sibutramine compared with placebo. However, orlistat was associated with gastrointestinal side-effects and sibutramine was associated with small increases in blood pressure and pulse rate. The authors concluded that longer and more methodically rigorous studies of anti-obesity drugs are needed to examine endpoints such as mortality and CVD morbidity to fully evaluate the benefit of these agents (Padwal et al, 2004).

Rimonabant became available in the UK in July 2006 and is licensed for use in obese, or overweight people, (BMI > 27 kg/m^2 and BMI ≥ 30 kg/m^2 respectively), with associated risk factors such as type 2 diabetes or dyslipidaemia. Rimonabant is the first selective cannabinoid receptor-1 (CB1) antagonist and works by modulating the endogenous endocannabinoid system, which is involved in regulating adipose deposition, energy balance, and glucose and lipid metabolism (Di Marzo and Matias, 2005).

The efficacy and safety profile of rimonabant was tested in the one-year, large-scale Rimonabant In Obesity (RIO)-Diabetes study, which involved 1045 overweight or obese people with type 2 diabetes (BMI 27–40 kg/m^2), with an HbA_{1c} of 6.5–10% who were already receiving metformin or sulphonylurea monotherapy. Results from baseline showed that, compared with placebo, rimonabant significantly reduced weight

Page points

1. Waist circumference should be used alongside BMI to calculate CVD risk.
2. Current pharmacotherapies, while highly effective in improving glycaemic control, potentially can cause weight gain, which is undesirable in obese patients.

Page points

1. Waist circumference should be used alongside BMI to calculate CVD risk.
2. Current pharmacotherapies, while highly effective in improving glycaemic control, potentially can cause weight gain, which is undesirable in obese patients.

(5.3 kg versus 1.4 kg for placebo; $P = <0.001$) and waist circumference (5.2 cm versus 1.9 cm for placebo; $P = <0.001$). Glycaemic control was also improved, mean baseline HbA_{1c} was 7.3% and change in HbA_{1c} was -0.6% for rimonabant compared with +0.1% for placebo ($P = <0.001$). Blood fats were also improved, with HDL cholesterol increasing by 15.4% for rimonabant versus 7.1% for placebo ($P = <0.001$) and triglyceride concentration decreasing by 9.1% for rimonabant versus a 7.3% increase for placebo ($P = <0.001$). Rimonabant was generally well tolerated but the incidence of adverse events – mainly depressed mood disorders, nausea and dizziness – was slightly greater in the treatment arm versus placebo. Hospital Anxiety and Depression scores were, however, similar across the three treatment groups (Scheen et al, 2006).

Conclusions

A high proportion of people with type 2 diabetes are abdominally obese and so are at a high risk of CVD. Waist circumference is a simple measurement which can be used alongside BMI within a primary care setting as part of an individual's CVD risk assessment, as supported by the recent JBS2 guidelines. While most of the pharmacotherapies currently used in the treatment of type 2 diabetes are highly effective in improving glycaemic control, most have potential weight gain as a side effect. Therefore, the challenge is to use appropriate pharmacological intervention that improves glycaemic control, decreases insulin resistance and induces sustainable weight loss in the treatment of abdominally obese people with type 2 diabetes. ■

Alberti KG, Zimmet P, Shaw J (2005) The metabolic syndrome-a new worldwide definition. *Lancet* **366**: 1059–62

Amos AF, McCarty DJ, Zimmet P (1997) The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabetic Medicine* **14** Suppl 5: S1–85

British Cardiac Society, British Hypertension Society, Diabetes UK et al (2005) Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91** Suppl 5: v1–52

Colhoun HM, Betteridge DJ, Durrington PN et al (2005) Rapid emergence of effect of atorvastatin on cardiovascular outcomes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetologia* **48**: 2482–5

Daousi Casson IF, Gill GV et al (2005) Prevalence of obesity in type 2 diabetes in secondary care: association with cardiovascular risk factors. *Postgraduate Medical Journal* **82**: 280–4

Despres JP, Golay A, Sjostrom L (2005) Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *New England Journal of Medicine* **353**: 2121–34

Despres JP, Lemieux I, Prud'homme D (2001) Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* **322**: 716–20

Diabetes UK (2006) *Diabetes: State of the Nations: Progress made in delivering the national diabetes frameworks. A progress report form Diabetes UK.* Diabetes UK, London

Di Marzo V, Matias I (2005) Endocannabinoid control of food intake and energy balance. *Nature Neuroscience* **8**: 585–9

Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. *Lancet* **365**: 1415–28

Ehtisham S, Hattersley AT, Dunger DB, Barrett TG (2004) First UK survey of paediatric type 2 diabetes and MODY. *Archives of Disease in Childhood* **89**: 526–9

Fasshauer M, Paschke R (2003) Regulation of adipocytokines and insulin resistance. *Diabetologia* **46**: 1594–603

Henry RR, Wiest-Kent TA, Scheaffer L et al (1986) Metabolic consequences of very-low-calorie diet therapy in obese non-insulin dependent diabetic and non-diabetic subjects. *Diabetes* **35**: 155–164

Hollander PA, Elbein SC, Hirsch IB et al (1998) Role of orlistat in the treatment of obese patients with type 2 diabetes: A 1-year randomized double-blind study. *Diabetes Care* **21**: 1288–94

'The challenge is to use appropriate pharmacological intervention that improves glycaemic control, decreases insulin resistance and induces sustainable weight loss in the treatment of abdominally obese people with type 2 diabetes.'

Kelley DE, Wing R, Buonocore C et al (1993) Relative effects of calorie restriction and weight loss in non-insulin dependent diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism* **77**: 1287–1293

Klein S, Fontana L, Young VL et al (2004) Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *New England Journal of Medicine* **350**: 2549–57

King H, Aubert RE, Herman WH (1996) Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 21: 1413–31

Lean ME, Powrie JK, Anderson AS, Garthwaite PH (1990) Obesity, weight loss and prognosis in type 2 diabetes. *Diabetic Medicine* **7**: 228–33

Maggio CA, Pi-Sunyer FX (1997) The prevention and treatment of obesity. Application to type 2 diabetes. *Diabetes Care* **20**: 1744–66

McNulty SJ, Ur E, Williams G (2003) A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin. *Diabetes Care* **26**: 125–31

National Institute for Clinical Excellence (2002) *Management of type 2 diabetes: management of blood glucose.* NICE, London

Norris SL, Zhang X, Avenell A et al (2005) Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database of Systematic Reviews* **2**: CD004095

Padwal R, Li SK, Lau DCW (2003) Long-term pharmacotherapy for obesity and overweight. *Cochrane Database System Reviews* **4**:CD004094

Pi-Sunyer FX (2000) Weight loss and mortality in type 2 diabetes. *Diabetes Care* **23**: 1451–2

Pouliot MC, Despres JP, Lemieux S et al (1994) Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *American Journal of Cardiology* **73**: 460–8

Purnell JQ, Weyer C (2003) Weight effect of current and experimental drugs for diabetes mellitus: from promotion to alleviation of obesity *Treatments in Endocrinology* **2**: 33-47

Ritchie SA, Ewart MA, Perry CG et al (2004) The role of insulin and the adipocytokines in regulation of vascular endothelial function. *Clinical Science (London)* **107**: 519–32

Scheen AJ, Finer N, Hollander P et al (2006) Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* **386**: 1660–72

Stumvoll M, Goldstein BJ, van Haeften TW (2005) Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* **365**: 1333–46

Thorne A, Lonnqvist F, Apelman J (2002) A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *International Journal of Obesity and Related Metabolic Disorders* **26**: 193–9

Van Gaal LF (1998) Relationship of body fat distribution pattern to atherogenic risk factors in NIDDM. Preliminary results. *Diabetes Care* **11**: 103–106

Van Gaal LF, Rissanen AM, Scheen AJ et al (2005) Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* **365**: 1389–97

Waine C (2006) A new therapeutic target for obesity: the CB1 receptors of the endocannabinoid system. *British Journal of Cardiology* Manuscript submitted

Wahrenberg H, Hertel K, Leijonhufvud BM et al (2005) Use of waist circumference to predict insulin resistance: retrospective study. *BMJ***330**:1363–4

Wajchenberg BL (2000) Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocrine Review* **21**: 697-738

Wang Y, Rimm EB, Stampfer MJ et al (2005) Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *American Journal of Clinical Nutrition* **81**: 555–63

Williamson DF, Thompson TJ, Thun M et al (2000) Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* **23**: 1499–504

Wing RR, Koeske R, Epstein LH et al (1987) Long-term effects of modest weight loss in type II diabetic patients. *Archives of Internal Medicine* **147**: 1749–53

Yusuf S, Hawken S, Ounpuu S et al (2005) Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* **366**: 1640–9

Zimmet P, Alberti KG, Shaw J (2001) Global and societal implications of the diabetes epidemic. *Nature* **414**: 782–7