Body composition and presentation of type 2 diabetes

Andrew Brewster

Article points

1. The presenting phenotype of type 2 diabetes is influenced by a person's gender, age and ethnic background.
2. Body composition, particularly in relation to the proportion of muscle mass to visceral fat, and degree of muscle fat accumulation plays an important role in the development of insulin resistance.
3. More emphasis should be placed on the management of abnormal body composition to target the underlying cause of insulin resistance, glucose dysregulation and the visceral fat-associated dyslipidaemia seen in patients with type 2 diabetes.

Key words

- Body composition
- Glucose metabolism
- Visceral fat
- Dyslipidaemia
- Skeletal muscle

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The presentation of type 2 diabetes is influenced by a person's gender, age and ethnic background. The difference in presentation depending upon age, sex and ethnicity may reflect alterations in body composition and body fat distribution among men and women at various ages, and may also reflect sex and ethnicity-related propensity to store visceral fat. The concept of identifying phenotypic presentations of type 2 diabetes in relation to body composition relies on separating glucose dysregulation and dyslipidaemia as distinct conditions. Each of these processes of disordered metabolism can be explained by a particular body phenotype and may occur together or, in isolation in the case of dyslipidaemia, years before the onset of glucose dysregulation.

The concept of metabolic syndrome involves the integration of glucose dysregulation and dyslipidaemia within the classification system of the syndrome (Alberti et al, 2006). It is well understood that quite different patients can fulfil the diagnostic criteria for metabolic syndrome with very disparate presenting features (Kahn et al, 2005; Cameron et al, 2004). The integration of glucose dysregulation with dyslipidaemia is perhaps rather counter-intuitive when one considers body composition and fat topography to understand the different phenotypic presentations of type 2 diabetes. Identification of the exact nature of altered body composition which exhibits itself as either glucose dysregulation or dyslipidaemia or both may enable a more tailored approach to the management of type 2 diabetes and optimise strategies for diabetes prevention. This article will review evidence: firstly, showing how body composition, particularly relating to differences in gender and in relation to age, affects the presentation of diabetes; and secondly, on the benefit of focusing management of diabetes on normalising body composition and maintaining lean tissue mass and aerobic capacity, and the available strategies for doing so.

Insulin resistance and characteristics of skeletal muscle

Insulin resistance is a key clinical feature of type 2 diabetes and frequently underlies the glucose dysregulation seen in these patients. Insulin resistance is linked to overweight and obesity, and occurs in both the liver and muscle. Elevated levels of plasma free fatty acids caused by accumulation of excess adipose tissue results in accumulation of lipid metabolites, such as fatty acyl CoA and diacylglycerol (DAG), in skeletal muscle cells. These lipid metabolites cause insulin resistance by interfering with the insulin signalling pathway (Petersen & Shulman, 2006).

In addition to the inhibition of insulin signalling by accumulation of lipids in skeletal muscle, there is evidence to support a link between insulin resistance and muscle quality and metabolic capacity of skeletal muscle. This was investigated in a study involving 62 older adults with type 2 diabetes, who received either strength training plus standard care or standard care alone for 16 weeks (Brooks et al, 2007). Strength training significantly improved muscle quality (strength per unit volume of muscle) compared with the control group (P<0.001) and was associated with improvements in overall glycaemic control (-1.0±0.2 in the strengh training group [8.7±1.0 at baseline and 7.6±1.5 at study end]), while there was no change in the control group (+0.4±0.3 [7.8±1.6 at baseline and 8.3±1.3 at study end]; P<0.001). Insulin resistance, as determined by the homeostasis model assessment of insulin resistance (HOMA-IR), was significantly reduced (P=0.05) in the group receiving strength training compared with controls.

The concept that insulin resistance is related to the physical fitness (maximal aerobic capacity [VO_{2max}]) of muscle as well as the amount of muscle tissue (muscle mass) was postulated as early as 1983. Levels of insulin resistance in male participants with different body compositions were compared: weight lifters (increased muscle mass, normal VO_{2max}); long-distance runners (normal muscle mass, increased VO_{2max}); and untrained controls (normal muscle mass and VO_{2max}; Yki-Jarvinen et al, 1983). It was found that weight lifters and runners had improved glucose metabolism compared with controls due to increased muscle mass and aerobic capacity (VO_{2max}), respectively.

It is well established that people with a diagnosis of type 2 diabetes have low VO_{2max} values when compared with healthy age-matched controls (Regensteiner et al, 1995; Katoh et al, 1996). Furthermore, evidence exists of a reduced functional exercise capacity in healthy individuals at high-risk of developing diabetes even before the appearance of glucose intolerance (Nyholm et al, 1996).

When considering insulin resistance in terms of lipid metabolite accumulation within skeletal muscle cells, it is interesting to note that the topographical distribution of body fat plays a key role in the development of insulin resistance. Accumulation of excess visceral fat, rather than subcutaneous fat, has been shown to correlate with insulin resistance (Pouliot et al, 1992). Expansion of the visceral fat depot in particular is related to elevated free fatty acid (FFA) levels, particularly in the portal circulation (Couillard et al, 1998), and may represent a marker of a concomitant propensity to store lipid with lean tissue (Unger, 2003).

Insulin resistance in muscle therefore appears to be related to a combination of lipid accumulation in muscle cells, the quality and fitness (aerobic capacity) of the muscle tissue, and the amount of muscle tissue present. This can be rationalised in terms of insulin resistance being a result of reduced peripheral glucose uptake and utilisation, principally by skeletal muscle. A person's overall glucose level will depend on these skeletal muscle-related factors together with the degree of pancreatic beta-cell deficiency, the degree of liver insulin resistance and associated hepatic glucose production.

Body composition, particularly in relation to muscle mass, visceral fat mass and lean tissue lipid accumulation therefore plays an important role in the development of insulin resistance. Differences in male and female muscle mass and fat distribution may explain the differences in diabetes presentation in men and women.

Body composition: Differences between men and women

Differences in body composition between males and females become apparent during puberty. Males show decreasing body fat through puberty and increasing lean tissue (muscle mass), a result of the action of testosterone (McCarthy et al, 2006). In contrast, females continue to gain body fat and have a greater percentage body fat than males at any BMI (See *Figure 1*).

Women have a greater percentage body fat and lower percentage muscle mass compared with men (Gallagher et al, 2000). When considering the factors that contribute to insulin resistance discussed above, this would appear to place

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2. It is well established that people with a diagnosis of type 2 diabetes have low VO_{2max} values when compared with healthy age-matched controls.
3. When considering insulin resistance in terms of lipid metabolite accumulation within skeletal muscle cells, it is interesting to note that the topographical distribution of body fat plays a key role in the development of insulin resistance.

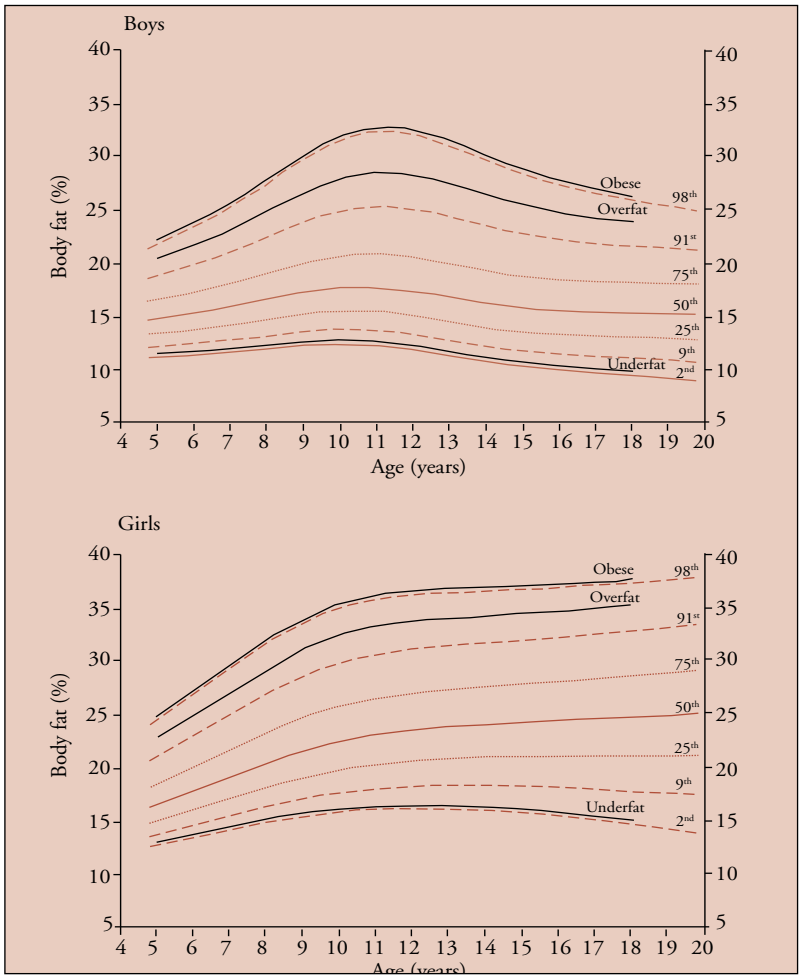

Figure 1. Percentage body fat for boys and girls between the ages of 5 and 18 years. Reprinted by permission from Macmillan Publishers Ltd: International Journal of Obesity (McCarthy et al, 2008), Copyright, 2008.

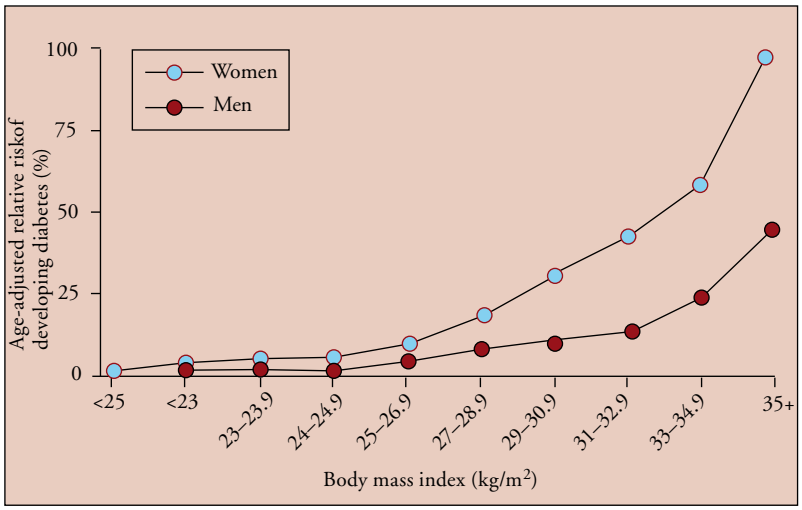

Figure 2. The relationship between obesity and BMI in men and women (adapted using data from Chan et al, 1994 and Colditz et al, 1995)

women at increased risk of developing insulin resistance and hence glucose dysregulation. The higher proportion of muscle tissue in men may confer some relative degree of protection against insulin resistance and glucose dysregulation. Indeed, studies investigating weight gain in men and women as a risk factor for diabetes indicate that women are significantly more likely than men to develop diabetes at any given BMI (*Figure 2*) (Chan et al, 1994; Colditz et al, 1995).

The concept that a higher proportion of muscle mass protects against insulin resistance is supported by studies involving androgen deficiency and testosterone replacement therapy. Testosterone levels correlate positively with lean muscle mass and negatively with fat mass (Vermeulen et al, 1999). Low testosterone levels in men predict insulin resistance, with the relative risk of developing diabetes decreasing with increasing levels of free testosterone and sex-hormone-binding globulin, which binds testosterone in the circulation (Haffner et al, 1996). People with Klinefelter's syndrome, a sex chromosome disorder associated with hypogonadism and infertility, are more likely to develop insulin resistance than those without (Bojesen et al, 2006). Interestingly, hypogonadotropic hypogonadism, manifest as reduced testicular function, is a common condition in male patients with type 2 diabetes (Dhinda et al, 2004).

Androgen replacement therapy in hypogonadal men increases lean muscle mass and decreases body fat, along with improving sexual function (Wang et al, 2000). Testosterone supplementation has been shown to improve glycaemic control in men with type 2 diabetes and androgen deficiency, and improves body composition by reducing abdominal obesity and increasing lean tissue mass (Boyanov et al, 2003; Kapoor et al, 2006). Improvements in insulin resistance have also been seen in patients with type 2 diabetes treated with low-dose growth hormone and diet modification (Nam et al, 2001). The improvements were also associated with a decrease in visceral fat and an increase in lean muscle mass.

Page points

1. So called 'diabetic dyslipidaemia' is characterised by raised triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol levels, along with an increased proportion of low-density lipoprotein (LDL) cholesterol being in the small, dense form.
2. This visceral-fat associated dyslipidaemia may be present many years before the associated classic diabetes presentation becomes apparent.

Body composition and dyslipidaemia

Obese men tend to store excess fat as abdominal visceral adipose tissue, in contrast to obese women who generally accumulate excess fat in the gluteofemoral region (Lemieux et al, 1993). This pattern of fat deposition places men at greater risk than women of developing what is known as 'diabetic dyslipidaemia'. Diabetic dyslipidaemia is characterised by raised triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol levels, along with an increased proportion of low-density lipoprotein (LDL) cholesterol being in the small, dense form. The accumulation of excess visceral adipose tissue and the subsequent release of FFAs into the circulation drives this pattern of dyslipidaemia (*Figure 3*).

Dyslipidaemia and signs of atherosclerosis have been observed in obese men of a young age. In the Pathological Determinants of Atherosclerosis in Youth (PDAY) study, arteries, blood and other tissues were examined from approximately 3000 people who died between the ages of 15 and 34 years (McGill et al, 2002). Even at this relatively young age, obesity was associated with dyslipidaemia and fatty streaks and lesions in the right coronary artery in men. There was little association between obesity and atherosclerosis in women, except those who were abdominally obese. Visceral-fat associated dyslipidaemia may be present many years before the associated classic diabetes presentation becomes apparent. In men, glucose dysregulation may therefore be regarded as the end-stage presentation of a chronic lipid disorder caused by the accumulation of visceral fat that occurred many years before the diagnosis of type 2 diabetes. Diabetic dyslipidaemia could therefore be seen as related to obesity. This view is supported by results from a survey of 7735 men aged 40–59 years showing that BMI is strongly associated with raised triglyceride and total cholesterol levels, and low HDL-cholesterol levels (Thelle et al, 1983). The term 'obesity-related dyslipidaemia', rather than diabetic dyslipidaemia may be more apt (*Figure 4*).

Body composition, ageing and diabetes

In contrast to the classical presentation of type 2 diabetes associated with abdominal obesity and

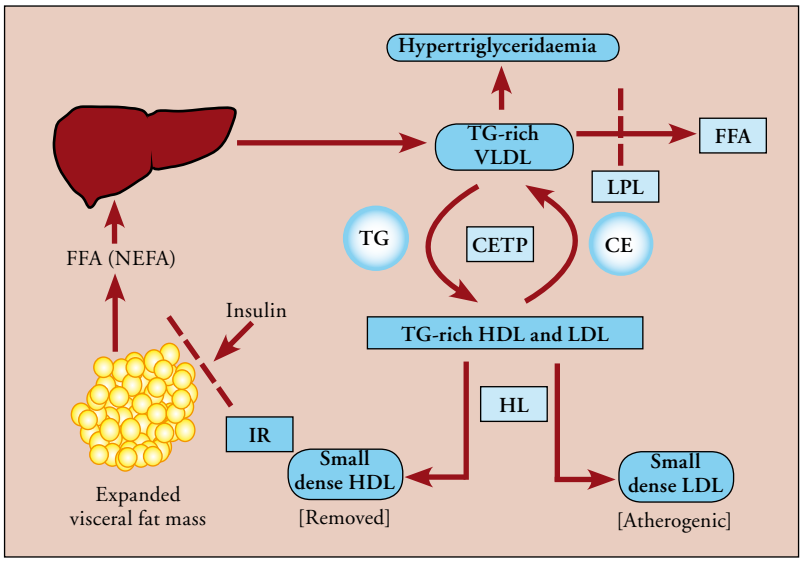

Figure 3. So called 'diabetic dyslipidaemia' is driven by increased release of free fatty acids (FFA) from expanded adipose tissue. CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein; HL = hepatic lipase; IR =insulin resistance; LDL = low-density lipoprotein; LPL = lipoprotein lipase; NEFA=nonesterified fatyy acids; TG =triglyceride; VLDL = very low-density lipoprotein.

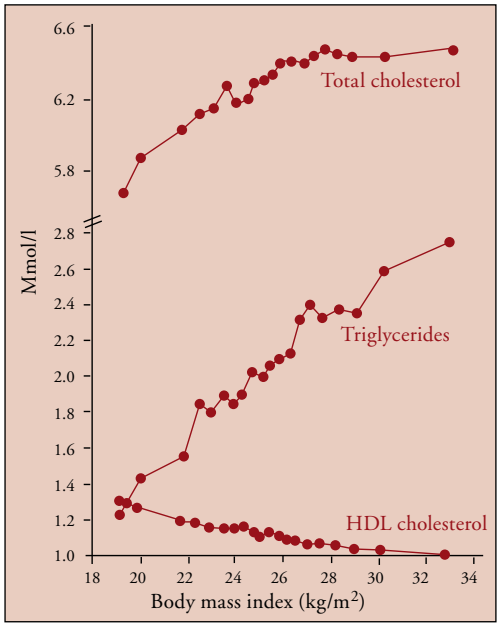

Figure 4. Dyslipidaemia in men, raised total cholesterol and triglyceride levels and reduced HDL-cholesterol levels, is strongly associated with increasing BMI. (Thelle et al (1983) Heart 49: 205–13. Reproduced with permission from the BMJ Publishing Group)

dyslipidaemia which tends to occur in midlife, the elderly can present with a pure glucose dysregulation phenotype in association with a normal BMI. Diabetic dyslipidaemia can be absent in such patients due to the absence of visceral fat accumulation.

Both men and women experience a loss of muscle mass and strength as they age. Older people with type 2 diabetes have lower muscle quality than those without diabetes (Park et al, 2006). Aging is characteristically associated with a replacement of skeletal muscle mass with increased fat mass. Aging can therefore be associated with increasing insulin resistance due to loss of muscle tissue. This process can occur in the context of a stable and entirely normal BMI.

In addition to a loss of muscle mass and quality (strength), reduced mitochondrial number and impaired function in skeletal muscle have been associated with insulin resistance. Mitochondrial oxidative and phosphorylation activity is reduced by as much as 40% in older people compared with young controls (Petersen et al, 2003). This suggests that insulin resistance in the elderly may be caused by increased accumulation of fatty acid metabolites in muscle cells, due not only to increased supply (FFA circulation) but also to reduced fatty acid oxidation via age-related reduction of mitochondrial function or number. Indeed, intensive lifestyle modification (physical activity and weight loss) can increase mitochondrial numbers and improve function in skeletal muscle of patients with type 2 diabetes (Toledo et al, 2007). This may partly explain the beneficial effects of lifestyle modification on insulin resistance.

Diabetes is a progressive condition because as people age, several physiological changes occur, each of which contribute to reduced insulin sensitivity: people exhibit increases in their body fat mass, which results in increased lipid accumulation in muscle cells; physical fitness falls, causing reduced muscle mass; and finally, mitochondrial numbers within muscle cells fall, reducing glucose utilisation. These age-related phenomenon in addition to loss of pancreatic function (via glucolipotoxicity) contribute to the progressive glucose dysregulation seen in type 2 diabetes.

Management of diabetes through altering body composition

If we accept that body composition plays a key role in the development of diabetes, prevention and treatment can be approached by improving body composition – reducing visceral adiposity and increasing lean muscle mass. Furthermore, understanding the different phenotypic presentations of diabetes in men and women can also help tailor therapy.

Lifestyle modification

Changes in lifestyle can delay the progression of diabetes. A recent retrospective study analysed the clinical records of 366 patients diagnosed with type 2 diabetes (Escobar et al, 2007). Patients who were overweight (BMI >25kg/m^2) and who reduced their BMI by 0.38kg/m^2 or more between 6 months and 12 months following diagnosis delayed the onset of pharmacotherapy (72 versus 42 months) compared with those who did not.

A number of trials have investigated the effect of three types of exercise (aerobic, resistance and combined exercise) in the management of diabetes. A meta-analysis including 27 such studies showed that all three types of exercise produced small to moderate improvements in glycaemic control as measured using HbA_{1c} (overall reduction following 12 weeks of training was a 0.8% reduction in HbA_{1c}; Snowling et al, 2006).

As discussed above, increasing muscle quality through strength training over a 16-week period has been demonstrated to reduce insulin resistance and improve glycaemic control (Brooks et al, 2007). Within this context it is useful to consider the important role of encouraging increased activity levels in both the prevention of type 2 dabetes and as a cornerstone in the management of established diabetes.

Lifestyle management has been shown to be more effective than metformin in preventing the onset of diabetes. In the US Diabetes Prevention Program, 3234 people without diabetes were assigned to lifestyle modification, metformin

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1. Lifestyle management has been shown to be more effective than metformin in preventing the onset of diabetes.
2. There are currently three pharmaceutical agents that are licensed in the UK for treating overweight and obesity: orlistat, sibutramine and rimonabant.
3. Exenatide is a welcome addition as an anti-diabetic medication which appears effective in promoting weight loss in patients with type 2 diabetes.
4. Surgery can provide an important treatment option for patients who are unable to maintain long-term weight loss through lifestyle management or pharmacotherapy.

or placebo for an average of 2.8 years (Knowler et al, 2002). Lifestyle modification reduced the incidence of diabetes by 58% and metformin by 31% compared with placebo. An interesting hypothesis to explain the greater efficacy of lifestyle intervention over metformin treatment is that one would expect lifestyle intervention to improve body composition, whereas the act of simply taking an insulin sensitizing drug would not be expected to have this positive impact on body composition.

Anti-obesity pharmacotherapy

There are currently three pharmaceutical agents that are licensed in the UK for treating overweight and obesity: orlistat, sibutramine and rimonabant. Orlistat reduces fat intake from the diet by approximately 30% by inhibiting lipase enzymes in the intestine. In randomised controlled trials, treatment with orlistat for 1 year produced weight loss greater than placebo by an average 2.7kg (Padwal et al, 2004). Greater reductions in LDL-cholesterol and triglyceride levels were also seen with orlistat, although levels of the cardioprotective HDL-cholesterol were also slightly reduced. Orlistat with lifestyle intervention has been shown to reduce the incidence of diabetes and improved weight loss over 4 years compared with lifestyle intervention alone (Torgerson et al, 2004).

Sibutramine is a monoamine reuptake inhibitor that acts centrally to reduce appetite. Patients treated with sibutramine experience an average 4.3kg greater weight loss than placebo in randomised controlled trials (Padwal et al, 2004). Improvements in triglyceride and HDL levels are seen with sibutramine treatment. In a study investigating the use of sibutramine in obese patients with type 2 diabetes, glycaemic control improved in parallel with weight loss. Patients who lost 5–10% of their body weight experienced a 0.7% reduction in HbA_{1c} and in those who lost 10%, HbA_{1c} fell by 1.2% (McNulty et al, 2003).

Rimonabant is the first in a new class of cannabinoid-1 receptor blockers. A meta-analysis of the four phase III trials involving rimonabant showed that patients treated with rimonabant (20 mg) experienced weight loss on average 4.9kg greater than those who received placebo over 1 year (Curioni et al, 2006). Rimonabant also has beneficial effects on waist circumference (abdominal obesity), HDL-cholesterol and triglyceride levels. In overweight or obese patients with type 2 diabetes, along with significant reduction in weight, rimonabant also improved glycaemic control, reducing HbA_{1c} by an average of 0.7% compared with placebo (Scheen et al, 2006). The improvements in these metabolic parameters were greater than could be accounted for by weight loss alone (Despres et al, 2005).

Anti-diabetic pharmacotherapy associated with weight loss.

Exenatide is a recently introduced subcutaneously administered adjunct treatment of type 2 diabetes. It is an incretin mimetic and exhibits activity similar to the naturally occurring hormone glucagon-like peptide 1 (GLP-1) which is secreted in the gut in response to food intake. Exenatide is a welcome addition as an anti-diabetic medication which appears effective in promoting weight loss in patients with type 2 diabetes. It is thought that the progressive reduction in body weight seen with exenatide treatment over an 82-week period, with a change from baseline of -4.4 ± 0.3kg, is primarily due to exenatide's actions of inducing satiety and therefore, reducing food intake. Interestingly, for an anti-diabetic medication, the magnitudes of improvements in HbA_{1c} and lipid profiles associated with exenatide treatment were seen in patients with the greatest weight reductions (Blonde et al, 2006).

Surgery

Surgery can provide an important treatment option for patients who are unable to maintain long-term weight loss through lifestyle management or pharmacotherapy. In a systematic review of 136 studies involving bariatric surgery, participants experienced a mean excess weight loss of 61.2%. A total of 76.8% of participants experienced complete resolution of their type 2 diabetes (Buchwald et al, 2004). A recent study investigated the effect of Rouxen-Y gastric bypass and biliopancreatic

diversion, two of the most effective procedures, on type 2 diabetes (Alexandrides et al, 2007). Overall, patients lost approximately 70% of their excess weight and maintained this weight loss over an average follow-up of 26 months. Type 2 diabetes resolved in 97% of patients and was improved in four patients who were on insulin therapy before the study started. LDL-cholesterol and triglyceride levels decreased and HDL-cholesterol levels increased significantly in all patients.

Impact on diabetes prevention and diabetes management

The evidence presented in this review article shows that significant benefits in terms of both preventing the development of diabetes and improving its management can be made by employing strategies that normalise body composition. Lifestyle modification has always formed the cornerstone of treating diabetes. This paper suggests that more emphasis should be placed on the management of abnormal body composition to target an underlying cause of insulin resistance: glucose dysregulation and the visceral fat-associated dyslipidaemia seen in patients with type 2 diabetes.

Conclusion

Men and women present with different diabetes phenotypes related to differences in muscle mass, muscle quality and fat topography. Women appear to be at greater risk of glucose dysregulation at any BMI compared with men. On the other hand, men tend to store excess fat in the abdominal region, placing them at increased risk of dyslipidaemia, with glucose dysregulation developing at a later stage of this disease process due to a degree of protection against glucose dysregulation afforded by an increased percentage of lean tissue mass. Strategies for preventing and treating diabetes should be aimed at restoring normal body composition and maintaining muscle mass and functional capacity of skeletal muscle. Physical activity to increase muscle mass and fitness, as well as weight loss through diet and pharmacological intervention to reduce visceral fat accumulation in particular, should therefore form an essential component of the treatment plan. ■

Competing interests

The author has received unrestricted educational grants from the following pharmaceutical companies to run an expert patient weight management service for his patients in primary care: Abbott, Novo Nordisk, Roche and Sanofi Aventis. The author has also received honoraria for undertaking presentations on behalf of Roche, Pfizer, Lilly, Takeda, MSD, Abbott and sanofi-aventis. He has also received consulting fees from Roche and sanofi-aventis.

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Physical activity to increase muscle mass and fitness, as well as weight loss through diet and pharmacological intervention to reduce visceral fat accumulation in particular, should therefore form an essential component of the treatment plan.

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