REVIEW

Diabetes Management

Targeting abdominal obesity in diabetes

Thinzar Min[1] & Jeffrey Wayne Stephens*[,1]

Practice points

- Abdominal obesity is generally defined by waist circumference.
- Ethnic specific cut-off values for waist circumference exist.
- Abdominal obesity is strongly associated with insulin resistance.
- Abdominal obesity is an independent risk factor for cardiovascular disease, Type 2 diabetes and metabolic syndrome.
- Waist circumference is a better predictive measure than BMI, in identifying obesity related morbidity and mortality.
- Lifestyle interventions: healthy balanced diet, increasing physical activity is key to preventing obesity epidemic.
- Pharmacological intervention has limited role.
- Surgical intervention: bariatric surgery has become a recommended treatment option for super obese individuals. Bariatric surgery has additional metabolic benefit such as remission of Type 2 diabetes.

SUMMARY Over recent years, there has been a better understanding of the role of that visceral adipose tissue plays in the pathogenesis of insulin resistance, Type 2 diabetes and the metabolic syndrome. Studies have consistently demonstrated that intra-abdominal fat accumulation, in other words, abdominal obesity is independently associated with Type 2 diabetes, hypertension, cardiovascular disease, nonalcoholic fatty liver disease and the metabolic syndrome. Furthermore, evidence supports the view that visceral adipose tissue is more closely associated with obesity related co-morbidities and mortality, compared with the total body adipose tissue (subcutaneous and visceral adipose tissue). The management of abdominal obesity involves a multidisciplinary team approach. Active healthy life style is a key in preventing obesity epidemic. Surgical intervention has become part of obesity treatment.

KEYWORDS
• adipose tissue • metabolic syndrome • obesity • Type 2 diabetes • visceral fat

What is abdominal obesity?

Abdominal obesity may be defined as an excess of intra-abdominal fat [1] and is sometimes referred to as central adiposity or visceral, android or male-type obesity. WHO defines 'overweight and obesity' as abnormal or excessive fat accumulation that may impair health [2]. Fat accumulates mainly in two locations, subcutaneously or visceral, with the majority being found in the former location (90% in females and 80% in males) and the remainder in the latter [3]. The BMI is the most widely used tool to identify and diagnose obesity. BMI is calculated as weight (in kilograms) divided by the height (in meters) squared. WHO and the NIH define overweight as a BMI between 25 and 29.9 kg/m^2 and obese as BMI greater than or equal to 30 kg/m^2 **(Box 1)** [2,4]. BMI is generally correlated

[1]Diabetes Research Group, College of Medicine, Swansea University, Wales, SA2 8PP, UK
*Author for correspondence: Tel.: +44 1792 704078; Fax: +44 1792 703214; J.W.Stephens@Swansea.ac.uk

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Box 1. Classification of body weight.

Classification of body weight

- Underweight
- Normal weight
- Overweight
- Obesity
- Obesity class I
- Obesity class II
- Obesity class III

BMI (kg/m²)

- <18.5
- 18.5–24.9
- 25–29.9
- ≥30
- ≥30–34.9
- ≥35–39.9
- ≥40

with body fat mass but does have limitations. The percentage of body fat varies with age, sex and ethnicity and therefore BMI may be an inaccurate measure of obesity in certain groups. In the Third National Health and Nutrition Examination Survey (NHANES III) [5], comprising of 13,601 subjects showed that 21% of men and 31% of women were obese using a BMI cut-off (BMI ≥30 kg/m^2), while 50% men and 62% women were obese using a body fat percentage cut-off (body fat percentage >25% in men and >35% in women). A BMI greater than or equal to 30 kg/m^2 has a good specificity but poor specificity and fails to identify greater than 50% of people with excess fat [5,6]. Almost all of the obese subjects had central adiposity (waist circumference >102 cm in men and >88 cm in women) but not BMI-defined obesity. Identifying abdominal obesity is particularly important in those with intermediate BMI ranges falling below 35 kg/m^2. Within the UK, NICE recommends using waist circumference in addition to BMI in people with BMI less than 35 kg/m^2 [7]. Ethnicity substantially influences BMI-defined obesity, as the proportion of visceral adipose mass differs significantly [8]. As a consequence, the WHO recommends a lower BMI for Asian populations [8].

How to diagnose abdominal obesity?

• Waist circumference

Waist circumference is the most widely used measure to quantify central obesity. In a study of 151 subjects, waist circumference was more closely associated with metabolic abnormalities compared with waist–hip ratio, with a waist circumference greater than 100 cm being associated with artherogenic metabolic changes [9]. Of note, different guidance provides different methods to quantify waist circumference. For example, WHO recommends that the measurement is made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest [10]. The NIH and NHANES III protocol recommend the superior aspect of the iliac crest as the site of measurement [4,5]. The NIH Multi Ethnic Study of Atherosclerosis (MESA) protocol measures waist circumference at the level of the umbilicus or navel [10]. Despite these different methods they do not appear to substantially influence the association between waist size and all-cause mortality, cardiovascular specific mortality and risk of cardiovascular disease and Type 2 diabetes [11]. All methods recommend using a flexible, stretch-resistant tape, which should be held snugly, but not constricting, and parallel to the floor at the level at which the measurement is made. The subject should be standing erect with their body weight equally distributed and the measurement recorded at the end of expiration. Furthermore, each measurement should be repeated twice and if the readings are within 1 cm of one another, the average should be calculated. If the difference between the two readings exceeds 1 cm, the two measurements should be repeated [10].

The cut-off values that define abdominal obesity also differ among guidelines. The International Diabetes Federation (IDF) defines central obesity as a waist circumference greater than 94 cm in Europid men and greater than 80 cm in Europid women. The IDF guidance also recommend ethnic specific cut-off values, for example, waist circumference greater than 90 cm for south Asian, Chinese and Japanese men [12]. The Adult Treatment Panel III (ATP III) use the cut-off value of greater than 102 cm for men and greater than 88 cm for women [13]. NICE [7] classifies three risk groups. For men, waist circumference less than 94 cm is low, 94–102 cm is high and greater than 102 cm is very high. For women, waist circumference less than 80 cm is low, 80–88 cm is high and greater than 88 cm is very high.

• Waist-to-hip ratio

Waist-to-hip ratio (WHR) is another commonly used anthropometric measure to identify central obesity. Waist circumference is measured as

described above with hip circumference recorded around the widest portion of the buttocks. The WHO guidance defines central obesity if waist to hip ratio greater than 0.90 in males and greater than 0.85 in females. WHR has been found to be a better screening tool for cardiovascular risk factors than BMI [14]; however, it does not appear to offer any distinctive advantage over waist circumference. No significant difference between waist circumference and WHR in the accuracy of risk factor prediction has been observed [15]. Using a ratio measure instead of single measurement is more prone to have interobserver variations and calculation errors. Since WHR is a ratio measure, there is a possibility that both lean individuals and obese individuals would have the same ratio.

- **The index of central obesity**

In 2007, Parikh *et al.* [16] published a novel parameter, the Index of Central Obesity (ICO) to define abdominal obesity. ICO is the ratio of waist circumference to height. They proposed the cut-off ICO greater than 0.5 irrespective of gender and race was more sensitive to identify central obesity, compared with waist circumference alone. Further studies are needed to validate the cut-off value of ICO and its predictive value.

- **Imaging**

Imaging methods are not routine in clinical practice to quantify abdominal obesity due to lack of accessibility and radiation exposure. CT and MRI are commonly used in research settings and both methods yield similar accuracy in estimating visceral adipose tissue volume [17]. The most common protocol for both CT and MRI is to obtain a single cross sectional image at the interspace between the fourth and fifth lumbar vertebrae and calculate visceral adipose tissue volume [3]. Hounsfield unit cut-off values of -190 to -30 are assigned for adipose tissue in the CT images. Manual identification of fat area is usually done by trained technicians for the MRI images. There is no standardized cut-off value for visceral adipose tissue volume. Studies have suggested that visceral fat volume greater than 100 cm^2 are associated with increased risk of obesity-related comorbidity and mortality [18,19].

Why target abdominal obesity?

The prevalence of obesity is increasing worldwide. In 2008, it was estimated that 1.4 billion people were overweight and more than 0.5 billion were obese. These figures are projected to rise to 2.3 billion and 0.7 billion respectively in 2015 [2]. In the UK in 2012, 62% of adult were overweight or obese, with 25% being obese and 2.4% having severe obesity [20]. Obesity is not only associated with Type 2 diabetes, hypertension, cardiovascular disease, metabolic syndrome and cancers, but also with significant mortality [21]. At least 2.8 million people die annually as a result of being overweight and obese [2]. Furthermore, obesity carries a substantial economic burden. In the UK, obesity was estimated to cost the National Health Service approximately GB£4.2 billion in 2007, with an estimated increase to GB£9.7 billion by 2050 with a wider cost of GB£49.9 billion to society [20].

Being overweight or obese (BMI ≥25 kg/m^2) is a major modifiable risk factor for Type 2 diabetes. The risk of developing Type 2 diabetes is associated with a history of childhood obesity and the duration and degree of obesity [20]. Data from the Health Survey for England 2011 show that 12.4% of obese people aged greater than or equal to 18 years have diagnosed diabetes, which is five-times that of healthy weight population [22]. Many previously published studies define obesity by BMI, which does not differentiate between lean body mass, fat mass and body fat distribution. Recent studies have shown the more important role of abdominal obesity in the development of cardiovascular disease, Type 2 diabetes and metabolic syndrome [23]. Clinical measurements of abdominal obesity such as waist circumference and WHR are independent predictors for obesity related morbidity and mortality [14,23–25]. Controversy exists on whether these parameters are more accurate than BMI in assessing obesity related health burden [26]. In a study of 843 African–American women, waist circumference was independently associated with a five-fold risk in hypertension and diabetes. Similar findings were also observed in men, where a waist circumference greater than or equal to 94 cm had a sensitivity of 84.4%, a specificity of 78.2%, positive predictive value of 82.9% and negative predictive value of 80.0% to identify Type 2 diabetes and future cardiovascular disease [27]. The Health of England survey also found that men with a raised waist circumference have a five-fold increased risk of diabetes and women a threefold increase in risk compared with lean counterparts [22].

Insulin resistance is one of the key pathophysiological processes in the development of

Type 2 diabetes and is strongly associated with visceral adiposity. Several mechanisms have been proposed to explain the association between obesity and insulin resistance [28–30]. In summary these include:

- Hepatic lipid excess. In the setting of obesity, the capacity to store lipid in adipose cells becomes limited. This excess lipids in the form of free fatty acids pass into the liver via portal circulation, leading to increased hepatic insulin resistance and hepatic gluconeogenesis. This phenomenum also leads to impaired beta cell insulin secretion and insulin resistance within skeletal muscle. The end result is hyperglycaemia due to reduced peripheral glucose uptake;
- Adipocytes are metabolically active cells, secreting many adipokines, such as leptin, adiponectin and resistin. Dysfunctional adipokine regulation due to obesity, leads to increased hepatic glucose production, reduced skeletal muscle glucose utilization, increased food intake and reduced energy expenditure;
- Adipocytes secrete not only adipokines, but also proinflammatory cytokines such as TNF-α and IL6 that are involved in the development of insulin resistance.

Obesity and insulin resistance are two main key components of the metabolic syndrome. Controversy exists on the use of this term and there is debate on whether the syndrome is simply a consequence of obesity per se. In fact, central obesity might be responsible for all the components of metabolic syndrome. Of interest, in a study of 14,924 participants from the NHANES III, Janssen *et al.* concluded that waist circumference, a measure of central obesity could explain obesity-related health comorbidities [31]. They investigated the relationship between BMI, waist size and combination of BMI and waist, with cardiovascular risk factors. Both BMI alone and waist circumference alone were found to be strong positive predictors of comorbidity. When both BMI and waist circumference were included, waist circumference remained a predictor of all comorbidities. This is in line with other studies, for example, Carey *et al.* [32] investigated the relationship between regional adiposity and insulin sensitivity in normal and overweight women. They observed that abdominal fat had a stronger association with insulin sensitivity than peripheral nonabdominal fat (r^2 = 0.79 vs 0.44) and furthermore increased abdominal fat was associated with increased fasting nonesterified fatty acids, lipid oxidation and hepatic glucose output. Of note, targeting subcutaneous fat as a treatment for metabolic dysfunction is not associated with any improvement. In a study by Klein *et al.*, 15 obese women underwent liposuction. After 12 weeks, subjects lost up to 48% of the subcutaneous fat volume, but there were no significant changes in insulin sensitivity, inflammatory markers such as CRP, IL6, TNF-α and adiponectin and cardiovascular risk factors [33]. The physiological importance of visceral adiposity is reflected in the more recent IDF definition for the metabolic syndrome **(Box 2)** which takes into account the importance of central obesity rather than BMI. In this definition, central obesity is the prerequisite to diagnose metabolic syndrome [12].

How to target abdominal obesity?

• Lifestyle intervention

The management of abdominal obesity and that of gross obesity share the same principle of leading an active and healthy lifestyle. Since obesity has become a global epidemic, preventive measures should be targeted to the population as a whole. Lifestyle modification (both diet and exercise leading to weight loss and increasing activity levels) can improve glucose tolerance and prevent progression from impaired glucose tolerance to Type 2 diabetes [34]. Furthermore, a large population-based study from the USA also observed that people with a low-risk lifestyle profile (nonsmoker, healthy diet, moderate alcohol consumption, engaging in physical activity and maintaining normal bodyweight) had a significantly lower risk of developing Type 2 diabetes [35]. Preventative measures should be implemented during childhood, as childhood obesity is strongly associated with obesity in adult [20].

• Dietary intervention

A healthy balanced diet is clearly a crucial factor in preventing obesity. Promoting healthy eating (healthy school meal for children, availability of healthy food choice at work-place restaurants and displaying calorie information on the food) is essential. The Scientific Committee on Nutrition (SACN) [20] recommends that the average intake of free sugars should be around 5% of dietary energy; the consumption of sugar-sweetened beverages should be minimized and fiber intake should increase to 30 g/day. Recent years have seen a variety of weight reducing diets including:

Box 2. The recent International Diabetes Federation definition of metabolic syndrome.

A person must have any two of the following four factors:

- Central obesity: defined as waist circumference ≥ 94 cm for Europid men and ≥80 cm for Europid women, with ethnicity specific values for other groups and
- raised triglyceride level: ≥150 mg/dl (1.7 mmol/l), or specific treatment for this lipid abnormality
- Reduced high-density lipoprotein cholesterol: <40 mg/dl (1.03 mmol/l) in males and <50 mg/dl (1.29 mmol/l) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose ≥100 mg/dl (5.6 mmol/l), or previously diagnosed Type 2 diabetes mellitus

Data taken from [12].

the intermittent fasting and the fast (5:2) diet, characterized by normal eating days and fasting days with 500–600 kcal/day; the Paleolithic diet (Stone Age diet), consisting foods that were available before agriculture was introduced; low glycemic index diet; Atkin diet, consisting high protein and low carbohydrate; Mediterranean diet; low calorie diet (800–1600 kcal/day) and very low calorie diet (<800 kcal/day) [36]. Studies have found short-term benefits of these diets with weight reduction up to 3 kg, and modest improvements in glycemic control and cardiovascular risk factors. To date there is no evidence which supports long-term reduction in weight and improved glucose control resulting from a dietary strategy [37]. NICE recommends a reduced calorie diet (600 kcal deficit per day) for obesity [7]. Low calorie diet and very low calorie diet should be considered to induce rapid weight loss in special circumstances, for instance: prior to bariatric surgery and knee replacement operation. Lim *et al.* found that rapid weight loss (15 kg over 8 weeks) could reduce liver fat by 30%, normalize insulin sensitivity and glucose homeostasis [38]. The long-term use of very low calorie diet carries high risk of nutritional deficiency and hence not advocated in routine practice.

• Physical activity

In the UK, the Department of Health provides guidance on the duration and intensity of physical activity for various age groups. Physical activity such as floor-based play and water-based activities in safe environments are encouraged for infants who are not yet walking. Young children who are able to walk unaided are recommended to be physically active at least 180 min, at intervals throughout the day. Children and young adults (5–18 years) are recommended to participate in at least 60 min per day of moderate intensity physical activity [39]. The recommendations for adults aged 19–64 years suggest undertaking both aerobic and muscle-strengthening activity during the week. Aerobic activity might include 150 min of moderate-intensity cycling or walking, or 75 min of vigorous-intensity activities such as running or a game of singles tennis. The duration of the activity can be divided into three 10 min sessions per day for 5 days a week [40]. Muscle-strengthening activities are recommended on greater than or equal to 2 days per week such that all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) are worked. NICE recommends a longer duration of physical activity for preventing of obesity (45–60 min per day) and maintaining weight loss (60–90 min per day) [7]. It would be crucial to set a realistic target and encourage people to reach that goal.

• Behavior interventions

The management of obesity is best undertaken in a multidisciplinary team. Behavior interventions by appropriately trained professionals should be part of obesity management. Behavior changes such as self-monitoring, assertiveness, cognitive restructuring, preventing relapse and strategies for dealing with weight regain are recommend in new NICE obesity guidelines [7].

• Pharmacological interventions

Once popular antiobesity drugs such as sibutramine, serotonin–norepinephrine reuptake inhibitor and rimonabant, a cannabinoid receptor blocker, were withdrawn due to cardiovascular safety and mental health safety issues. Orlistat, an intestinal lipase inhibitor that prevents fat digestion and absorption from gastrointestinal tract, is currently the only licensed medication for obesity in the UK. In a double-blind randomized control trial involving 3305 patients, mean weight loss as well as incidence of Type 2 diabetes after 4 years was

Box 3. The NICE recommendations for bariatric surgery.

- BMI ≥50 kg/m^2, the option of choice.
- BMI ≥40 kg/m^2.
- BMI 35-40 kg/m^2 with other significant disease: T2DM, high blood pressure.
- BMI ≥35 kg/m^2 or over who have recent-onset T2DM an expedited assessment for bariatric surgery is recommended.
- BMI of 30-35 kg/m^2 with recent-onset T2DM.
- Lower BMI for individuals of Asian family origins and recent onset T2DM.

T2DM: Type 2 diabetes.
Data taken from [7].

significantly lower in orlistat-treated group [41]. Many guidelines recommend that orlistat is used in individuals with a BMI greater than or equal to 30 kg/m^2 or in individuals with a BMI greater than or equal to 28 kg/m^2 in the presence of other risk factors such as Type 2 diabetes, hypertension or hypercholesterolemia [42]. Treatment should only be continued beyond 3 months only if the patient has lost at least 5% of initial body weight since commencing the drug and should be continued longer than 12 months after discussing potential benefits and side effects with the patient. The side effects are gastrointestinal upset including steatorrhea and fat-soluble vitamin deficiency.

GLP-1 analogs are now established treatments for Type 2 diabetes and are also associated with weight loss ranging from 3-4 kg weight [43,44]. In a randomized double-blind placebo control, liraglutide was compared with orlistat and placebo. At year 2, subjects treated with liraglutide (2.4/3.0mg) lost 3.0 kg more weight than orlistat and were able to maintain weight loss of 7.8 kg from baseline. The prevalence of prediabetes and metabolic syndrome was also lower [45]. Currently, GLP-1 is recommended for individuals with inadequate glycemic control and high BMI. Recently, the US FDA advisory panel recommended approval for liraglutide 3 mg daily as an antiobesity medication [46].

• Surgical interventions

Bariatric surgery is a recommended treatment option for obesity. Common bariatric surgical procedures include laparoscopic adjustable banding, Roux-en-Y gastric bypass, sleeve gastrectomy and bilio-pancreatic diversion with duodenal switch. Bariatric surgery has been found to have significant beneficial effects in relation to metabolic dysfunction in addition to weight loss. Studies have shown that bariatric surgery is superior to conventional medical treatment and effective in achieving remission or significant improvement in hyperglycemia in people with Type 2 diabetes [47,48]. Furthermore, bariatric surgery is associated with

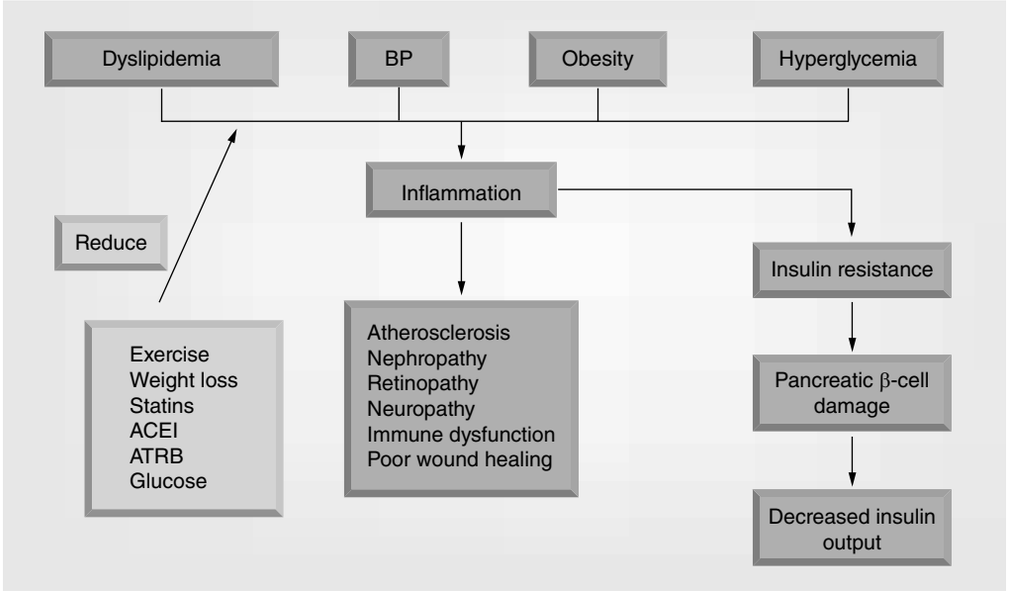

Figure 1. The link between metabolic syndrome, inflammation and cardiovascular disease.
ACEI: Angiotensin-converting enzyme inhibitor; ATRB: Angiotensin II receptor blocker; BP: Blood pressure.

lower incidence of newly diagnosed Type 2 diabetes up to 7 years after operation [49]. Within the UK, NICE recommends bariatric surgery as an option for weight loss management if certain criteria are fulfilled as shown in **Box 3**. However, bariatric surgical procedures are not without risk. These include risk associated with general anesthesia, operation related morbidity and mortality and a high risk of nutritional deficiency. Adherence with recommended diet and commitment to lifelong follow-up are mandatory. Proper patient selection, preoperative and postoperative psychological counseling and good follow-up plan are key to the success of bariatric surgery in treating obesity and its related co-morbidity.

• Managing cardiovascular risk factors in the obese patient

In addition to managing and treating obesity *per se*, therapies to reduce cardiovascular risk should be optimized in these patients [50,51]. As shown in **Figure 1**, statins and blood glucose should be optimized for patients with diabetes according to local guidance. Blood pressure control should be optimized with angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blocking agents (ATRB) and other agents as per local guidance. Aspirin use should also be considered but controversy exists in relation to this as co-morbidities associated with aspirin use may outweigh any benefit [51]. Nevertheless, cardiovascular risk reduction should be optimized with these proven agents [51].

Conclusion

Features of the metabolic syndrome such as abdominal obesity, impaired glucose regulation, elevated blood pressure and dyslipidemia, all contribute to the ultimate complication of cardiovascular disease. There is emerging evidence that obesity (and the metabolic syndrome) is an 'inflammatory syndrome', which is associated with significant metabolic dysfunction and cardiovascular disease **(Figure 1)** [52,53]. Obesity, diabetes/prediabetes, hypertension and dyslipidemia are all associated with low-grade chronic inflammation, which in turn leading to atherosclerosis, retinopathy, nephropathy, neuropathy, immune dysfunction and poor wound healing, features of Type 2 diabetes. Inflammation is also associated with insulin resistance as well as pancreatic β-cell exhaustion and subsequent impaired insulin secretion and hyperglycemia. Multifactorial intervention: targeting obesity, hypertension, diabetes and dyslipidemia are therefore essential and the use of statins, blood pressure medications, aspirin and diabetes therapies should be used to achieve recommended targets.

Future perspective

Our understanding of the pathophysiology of central obesity, associated complications and the roles of therapeutic options such as bariatric surgery has increased during the last decade. Alongside this the prevalence of obesity has also increased worldwide. The future challenge in targeting central obesity will clearly be in the prevention of obesity and in those who are already obese to develop effective therapies to reduce food intake and facilitate energy expenditure. Many therapeutic options are under investigation [54] but the challenge will be to see if these translate to clinical effectiveness.

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