

Abdominal Adiposity: Early Intervention and Therapeutic Options

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Abdominal obesity, especially visceral adipose tissue (VAT), increases the incidence of a cluster of metabolic disturbances (the so-called metabolic syndrome), type 2 diabetes, and associated cardiovascular risk. Not only is abdominal obesity a marker of a dysmetabolic profile, but VAT also appears to be a causal factor for morbidity and premature mortality, both by classic mechanisms (ie, dyslipidemia, hypertension, and glucose dysmetabolism), as well as less conventional mechanisms (ie, low adiponectin levels and high proinflammatory cytokine levels that promote insulin resistance and endothelial dysfunction). Because abdominal obesity is increasingly seen in young people, early intervention is mandatory to stop the cycle that leads to cardiometabolic risk. Obesity should be considered a chronic disease of multifactorial etiology, and treatment must be maintained for life—first with lifestyle interventions (energy-reduced diet and increased physical activity) and then with pharmacologic approaches (eg, orlistat, sibutramine, or rimonabant), when necessary. Beneficial metabolic effects may result from even moderate weight loss and are attributed primarily to a predominant reduction in VAT. Finally, special attention should be paid to possible additional positive effects beyond weight reduction, as especially demonstrated with the CB₁ antagonist rimonabant. (*Clinical Cornerstone*. 2008;9[Suppl 1]:S20–S27)
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Obesity is a growing problem that is reaching epidemic proportions worldwide and is associated with an increased risk of premature death in both men and women.¹ The INTERHEART case-control study emphasized the crucial role of abdominal obesity in the risk of myocardial infarction.² In addition to total body fatness, the accumulation of abdominal fat independently increases the risk of metabolic abnormalities³ and cardiovascular disease (CVD).⁴ The recent International Day for the Evaluation of Abdominal Obesity (IDEA) survey among 168,000 primary care patients in 63 countries found that waist circumference was strongly linked to CVD and especially to type 2 diabetes mellitus (DM).⁵ Strategies to address this global problem are required to prevent an epidemic of morbidity and mortality related to abdominal obesity.

The goals of obesity treatment have changed dramatically in the past 2 decades, moving from the objective of reaching an ideal body weight toward the attainment of a healthier body weight.⁶ Interestingly, modest weight loss, as low as 5% to 10% of initial body weight, can reduce or eliminate disorders associated with obesity, especially

the components of metabolic syndrome and type 2 DM.⁷ The proposed explanation is that such moderate weight loss is sufficient to induce a 25% to 30% reduction in visceral adipose tissue (VAT) and, thus, improvement in the various associated metabolic disturbances.⁸

The objectives of the present concise review are to summarize the rationale for early intervention targeting abdominal obesity and to describe briefly the available tools, including lifestyle interventions and pharmacologic agents that can help to reduce cardiometabolic risk.

KEY POINT

The goals of obesity treatment have changed dramatically in the past 2 decades, moving from the objective of reaching an ideal body weight toward the attainment of a healthier body weight.

KEY ROLE OF ABDOMINAL ADIPOSITY Metabolic Syndrome and Type 2 Diabetes

Although obesity is a risk factor for insulin resistance, type 2 DM, and CVD, not every overweight/obese patient is at high risk. For any given amount of total body fat, individuals with a selective excess of abdominal adipose tissue (mainly intra-abdominal or VAT) are at substantially higher risk of being characterized by insulin resistance, the components of metabolic syndrome, and type 2 DM.^{3,9}

There is ample evidence that impaired fatty acid metabolism could contribute to the insulin-resistant state observed among individuals with visceral obesity. However, there is also evidence that adipose tissue not only is involved in the storage and mobilization of lipids, but also that it is a remarkable endocrine organ releasing numerous molecules, including various hormones (eg, leptin, adiponectin) and several proinflammatory cytokines (eg, interleukin-6, tumor necrosis factor- α). There is also evidence of macrophage infiltration of VAT, which could contribute to the inflammatory profile (ie, high levels of C-reactive protein [CRP]) that has been reported in abdominally obese patients. Compared with levels of proinflammatory adipokines, which are elevated in obese individuals, adiponectin levels are reduced in these individuals, particularly among those with excess VAT. Because adiponectin improves insulin signaling, the low adiponectin levels observed in visceraally obese patients could be one of the key factors responsible for their diabetogenic and atherogenic metabolic risk factor profile. Both the altered fatty acid metabolism and the endocrine function hypotheses imply that VAT may be causally involved in the pathophysiology of the components of metabolic syndrome often found in patients with abdominal obesity.^{3,9}

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VAT may be causally involved in the pathophysiology of the components of metabolic syndrome often found in patients with abdominal obesity.

Cardiovascular Disease

Obesity is now recognized as a major modifiable risk factor for coronary heart disease.¹⁰ Different mecha-

nisms linking obesity to CVD have been postulated.⁴ Obesity, primarily abdominal adiposity, may influence classic CVD risk factors, such as hypertension, lipid abnormalities, and dysfunctions in glucose metabolism. Obesity increases the prevalence of less conventional risk factors, including several already mentioned cytokines and inflammatory markers, and elevates levels of intercellular adhesion molecule-1, contributing to endothelial dysfunction, as well as plasminogen activator inhibitor-1, leading to a procoagulatory and hypofibrinolytic state. In addition to its antidiabetic effect, adiponectin has important anti-inflammatory and antiatherogenic properties through various complex mechanisms. Therefore, low adiponectin levels associated with abdominal obesity may contribute to increased CVD risk. Finally, oxidative stress has been proposed to be a potential pathogenic mechanism linking obesity and insulin resistance with endothelial dysfunction, promoting atherosclerosis. When classic risk factors, including smoking, are superimposed on the insulin-resistant state of abdominal obesity, these risk factors may further increase the less conventional risk factors and exacerbate existing cardiovascular problems.⁴

RATIONALE FOR EARLY INTERVENTION Increased Prevalence of Abdominal Adiposity in Young People

Weight gain during childhood and adolescence or during early adult life seems to have a significant impact on the development of type 2 DM, metabolic syndrome, and CVD, even within the normal body mass index (BMI) range.¹¹ High visceral and low abdominal subcutaneous fat stores in the obese adolescent are a determinant of an adverse metabolic phenotype.⁹ These adolescents are not necessarily the most severely obese, yet they suffer from severe metabolic complications of obesity and are at high risk for developing metabolic syndrome.⁹ Preventing childhood overweight and obesity has become a major public health issue in developed and developing countries.¹¹

Stopping the Cycle of Obesity and Disease Development and Progression

Although excess VAT accumulation is associated with various diabetogenic and atherogenic abnormalities, an important question is whether VAT is a causal factor or simply a marker of a dysmetabolic profile.³ Fat in the liver is now considered a key factor in insulin resistance and a major player in glucose and lipid metabolic distur-

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bances.¹² If VAT is one of the most important underlying components leading to various CVD risk factors (eg, type 2 DM, atherogenic dyslipidemia, hypertension), an appealing option would be to target the abdominal obesity at an early stage. Ideally, this option should be implemented before the development of associated complications and disease progression to foster better clinical outcomes and to reduce the cost in health, time, quality of life, and money for the separate treatment of each of these major risk factors as well as the management of subsequent CVD complications. This strategy appears to be especially important in young overweight/obese individuals who are at risk for developing various metabolic disorders, including metabolic syndrome, type 2 DM, and premature CVD.¹¹

TREATMENT OPTIONS

The current epidemic of metabolic syndrome and type 2 DM is a direct result of our energy-dense diet and affluent sedentary lifestyle. This positive energy balance leads to abdominal obesity and insulin resistance. In overweight/obese individuals, the first objective is to achieve and maintain weight reduction, especially in the presence of metabolic syndrome¹³ and type 2 DM.^{14–16} This can be accomplished by achieving and sustaining a negative energy balance through a reduced-calorie diet and/or increased physical activity, as well as pharmacologic treatment, when necessary.¹⁷ Abdominal obesity, specifically VAT, is a target for early intervention in managing cardiometabolic risks in overweight and obese individuals (**Figure**). Beneficial effects may be partly weight-loss-dependent and partly weight-loss-independent. However, increasing evidence suggests that some favorable metabolic effects may occur beyond and independent of weight loss.^{18,19}

Lifestyle Modifications

The primary approach for achieving weight loss, in the vast majority of cases, is lifestyle modification, including a reduction in energy intake and an increase in physical activity.^{17,20}

Diet

There is no evidence to suggest that specific components of the diet (ie, carbohydrate, fat, protein, vitamins, micronutrients) influence the ways in which food energy is absorbed or used. Therefore, the main dietary approach for reducing weight is to reduce the total amount of calories consumed, and this is best achieved by a reduction in the amount of fat in the diet and calories from soft drinks. A moderate decrease in caloric balance (500–1000 kcal/d) will result in a slow but progressive weight loss.²¹ In addition, evidence suggests that the components of diet currently recommended as healthy—including low consumption of saturated and trans fats, intake of carbohydrates that are rich in dietary fiber, high fruit and vegetable intake, and the inclusion of low-fat dairy foods—are likely to protect against metabolic syndrome.²² However, even if dietary efforts are the primary treatment approach for people who are overweight or obese, dietary counseling interventions generally produce only modest weight loss that diminishes over time, as emphasized in a recent meta-analysis.²³

Exercise

Most obesity studies have not adequately measured physical activity and functional capacity, and the independent contributions of “fitness” versus “fatness” to health risks associated with obesity are still being debated.²⁴ Nonetheless, the role of physical activity as a treatment and/or preventive strategy for combating obesity has been the subject of substantial research. A systematic review of the literature concluded that limited evidence from a number of studies that used imaging techniques to quantify changes in abdominal obesity suggests a beneficial influence of physical activity on reduction of abdominal fat and VAT in overweight and obese subjects.²⁵ Reductions in VAT and total abdominal fat may occur in the absence of changes in body mass and waist circumference. Because the deposition of fat in the abdomen and in nonadipose tissues such as liver¹² and muscle²⁶ plays a major role in the development of obesity-related health risks, these depots have

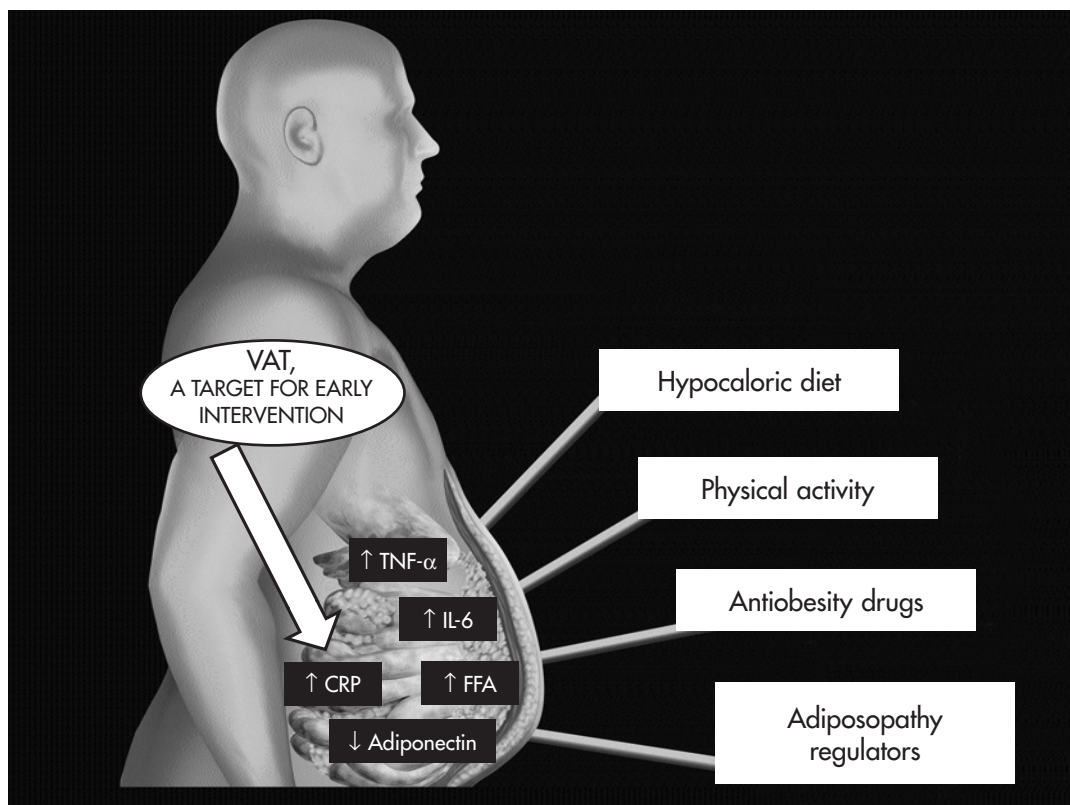


Figure. Abdominal obesity, specifically visceral adipose tissue (VAT), is a target for early intervention in managing cardiometabolic risks in overweight/obese individuals. Beneficial effects may be partly weight-loss-dependent and partly weight-loss-independent. ↑ = elevated; TNF- α = tumor necrosis factor- α ; IL-6 = interleukin-6; CRP = C-reactive protein; FFA = free fatty acids; ↓ = reduced.

emerged as alternative targets for obesity treatment and may partly explain the utility of physical activity with only minimal or no weight loss in the treatment of obesity.¹⁹ However, more rigorous studies are needed to confirm these observations.

Pharmacologic Therapy

Pharmacologic therapy can be offered to obese patients who have failed to achieve their weight loss goals through diet and exercise alone,²⁷ and it should be considered for patients with either a BMI >30 kg/m² or a BMI >27 kg/m² with obesity-related risk factors or disease. A goal of researchers has been to develop safe and effective antiobesity drugs, analogous to the development of treatments for hypertension, dyslipidemia, and diabetes. An emerging concept is that the development of antiobesity agents must not only reduce fat mass (adiposity) but also correct fat dysfunction (adiposopathy, ie, functional [metabolic, hormonal, inflammatory] disturbances of

adipocytes).^{17,28} Because it is now recognized that obesity is a chronic disease, only those approaches that induce safe long-term weight reduction should be considered valuable treatment strategies for obese subjects. Clinical trials have investigated body weight changes, as well as ancillary markers for cardiovascular risk factors (eg, hypertension, type 2 DM, dyslipidemia, elevated CRP levels). Special attention should be paid to the beneficial metabolic effects resulting from even moderate weight loss and to possible additional effects beyond weight reduction.^{17,18} Because only very few controlled trials have assessed early pharmacologic options for overweight adolescents, further research is required for pharmacotherapy in young people to prove its long-term efficacy and safety.²⁹

Classic Antiobesity Agents

Recent systematic reviews and meta-analyses have assessed both the safety and efficacy of the 2 drugs cur-

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rently used in the treatment of obesity in adults—orlistat, a gastric and pancreatic lipase inhibitor that reduces fat absorption from the gut, and sibutramine, a combined norepinephrine and serotonin reuptake inhibitor that regulates food intake.^{30,31}

The most important study conducted with orlistat was the 4-year XENical in the prevention of Diabetes in Obese Subjects (XENDOS) placebo-controlled trial.³² This trial demonstrated that the modestly greater weight reduction associated with orlistat was sufficient to reduce the cumulative incidence of type 2 DM by 37% ($P = 0.003$). This reduction was especially remarkable in obese patients with impaired glucose tolerance at baseline (-52% ; $P < 0.02$). Significant and sustained reductions in cardiovascular risk factors, such as arterial blood pressure and lipid levels (primarily total cholesterol and low-density lipoprotein [LDL] cholesterol), were also observed in the orlistat group compared with those in the placebo group (all, $P < 0.01$). XENDOS was the first study to demonstrate that the addition of an antiobesity agent is able to reduce the progression to diabetes in obese subjects compared with lifestyle changes alone. Unfortunately, the gastrointestinal tolerability of orlistat is rather poor, explaining the high dropout rate in all trials performed with this drug. A recent 1-year study showed that, in combination with diet, exercise, and behavioral modification, orlistat significantly improves weight management in obese adolescents compared with placebo, with a greater reduction in BMI (placebo-subtracted, -0.86 kg/m²; $P = 0.001$) and waist circumference (-1.45 cm; $P < 0.05$), a difference explained by changes in fat mass.^{29,33}

The Sibutramine Trial of Obesity Reduction and Maintenance (STORM) was the longest randomized clinical trial performed with sibutramine.³⁴ An individualized management program combining restricted diet and sibutramine therapy achieved weight loss in $\sim 75\%$ of obese patients after 6 months and sustained weight loss in $\sim 50\%$ of patients who continued therapy for 2 years. Most of the beneficial metabolic effects observed with sibutramine appeared to result from the drug-induced weight loss. Interestingly, sibutramine treatment was associated with a remarkable increase in high-density lipoprotein (HDL) cholesterol levels compared with placebo after 2 years (20.7% vs 11.7%; $P < 0.001$), exceeding that expected from weight loss alone. In contrast, sibutramine may be associated with a slight increase in heart rate and arterial blood pressure. The overall cardiovascular safety and efficacy of the drug is currently being investigated in the Sibutramine Cardiovascular and Diabetes Outcome Study (SCOUT). Preliminary data gathered during the initial single-blind, 6-week lead-in period with sibutramine plus weight management were recently reported.³⁵ In a total of 10,742 overweight/obese subjects with an increased risk of CVD, significant reductions in body weight (mean, -2.2 kg), waist circumference (-2 cm), and systolic blood pressure (-3 mm Hg) were observed (all, $P < 0.001$); a mild increase in pulse rate ($+1.5$ beats/min) was also observed ($P < 0.001$). According to these preliminary data, 6 weeks of treatment with sibutramine appears to be efficacious, tolerable, and safe in a high-risk population for whom sibutramine is usually contraindicated. Experience with sibutramine in adolescents is still limited.²⁹ However, a 6-month, placebo-controlled trial revealed that sibutramine therapy plus diet and exercise induced significantly more weight loss in obese adolescents than did placebo (-10.3 vs -2.4 kg; $P < 0.001$), with a good safety and tolerance profile.³⁶

CB₁ Antagonists

Rimonabant, a new compound acting as a selective blocker of CB₁ receptors of the endocannabinoid system, raises much interest because it promotes weight reduction by a central effect and also exerts peripheral effects targeting cardiometabolic risk.^{37,38}

The Rimonabant in Obesity (RIO) and related disorders program comprises 4 large-scale clinical trials assessing both the efficacy and safety of rimonabant (5 or 20 mg/d vs placebo) in >6600 overweight/obese adult

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individuals.³⁹ Therapy with rimonabant 20 mg combined with diet was associated at year 1 with significantly greater weight loss (placebo-subtracted, -4.7, -4.7, -5.4, and -3.9 kg in RIO-Europe, RIO-North America, RIO-Lipids, and RIO-Diabetes, respectively; all, $P < 0.001$) and greater reductions in waist circumference (-4.2, -3.6, -4.7, and -3.3 cm vs placebo, respectively; all, $P < 0.001$), clinical markers of abdominal obesity. After 1 year, 2- to 3-fold more patients achieved a weight reduction $\geq 5\%$ or $\geq 10\%$ of initial body weight in the rimonabant 20-mg group than did those in the placebo group. RIO-North America and RIO-Europe demonstrated that these favorable effects on body weight (-3.6 and -4.2 kg, respectively; $P < 0.001$) and waist circumference (-2.8 and -3.9 cm, respectively; $P < 0.001$) were maintained during the second year of treatment. Rimonabant was also associated with consistent increases in HDL cholesterol (placebo-subtracted at year 1, +7.2% to +8.9%; $P < 0.001$) and reductions in triglycerides (-12.4% to -16.4%; $P < 0.001$), changes that persisted after 2 years (+6.3% to +10.0% and -8.5% to -14.0%, respectively; $P < 0.001$).

Rimonabant has shown sustained efficacy in the management of multiple cardiometabolic risk factors,³⁹⁻⁴¹ such as insulin resistance, glucose intolerance, atherogenic dyslipidemia (low HDL cholesterol levels, high triglyceride levels, and increased numbers of small dense LDL particles), inflammatory markers (high CRP levels), low adiponectin levels, and high arterial blood pressure, in high-risk nondiabetic^{39,40} and diabetic^{39,41} populations. All studies in the RIO program³⁹ demonstrated that a substantial proportion (45%-57%) of the improvements in cardiometabolic risk factors (HDL cholesterol, +16.2% [SD, 19.1%]; adiponectin, +2.2 [2.5] $\mu\text{g/mL}$; triglycerides, -7.2% [39.5%]; glycosylated hemoglobin [HbA1c], -0.6% [0.8%]; fasting insulin, -0.6 [10.5] $\mu\text{IU/mL}$; insulin

resistance index, -0.2 [2.9]; all, $P < 0.001$) produced by rimonabant (20 mg) therapy exceeds the levels that would be expected solely from the degree of weight loss, probably reflecting a direct pharmacologic effect of the drug in peripheral tissues.

The ability of rimonabant to (1) reduce abdominal obesity and associated lipid disorders, (2) prevent the development of type 2 DM in abdominally obese patients with impaired glucose tolerance, (3) reduce surrogate markers of atherosclerosis, and (4) reduce the incidence of CVD complications in high-risk patients is currently being investigated in several large-scale clinical trials (ADAGIO; RAPSODI; AUDITOR; and CRESCENDO, respectively). The recently published Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study (STRADIVARIUS)⁴² in patients with abdominal adiposity and coronary artery disease confirmed favorable effects of rimonabant 20 mg on weight loss (-3.8 kg) and waist reduction (-3.5 cm) and significant improvements of various cardiometabolic risk factors, including HDL cholesterol (placebo-subtracted, +15.5%), triglycerides (-14.3%), and CRP (-19.4%) (all, $P < 0.001$). After 18 months of treatment, the study failed to show an effect for rimonabant on progression of coronary atherosclerosis for the primary end point (percent atheroma volume); however, it did show a favorable effect on the secondary end point (reduction in total atheroma volume assessed by coronary intravascular ultrasonography), which appears promising.

The most frequent side effects of rimonabant include mild nausea, dizziness, anxiety, and mood disorders³⁹⁻⁴¹; therefore, rimonabant is contraindicated in patients with antecedents of depression or in those taking antidepressive agents. Until now, there have been no studies evaluating the efficacy and safety of rimonabant in overweight/obese children or adolescents, a population for which pharmacotherapeutic options raise increasing interest.²⁹ Rimonabant is not yet approved for use in the United States.

Surgery

The contrasting effects of various surgical procedures on the metabolic profile have underscored the crucial role of intra-abdominal adipose tissue (ie, VAT) rather than subcutaneous abdominal adipose tissue. Indeed, whereas large-volume liposuction that reduces abdominal subcutaneous fat depots by 8 to 10 kg has almost no favorable effects on the metabolic profile,⁴³ omental fat reduction (correspond-

ing to only 0.8% of total body fat) in connection with adjustable gastric banding results in a dramatic improvement in insulin resistance and associated glucose disturbances.⁴⁴ The improvements in oral glucose tolerance, insulin sensitivity, fasting plasma glucose, and fasting insulin were 2 to 3 times greater in omentectomized subjects as compared with control subjects (P from 0.009 to 0.04). Bariatric surgical procedures (ie, gastroplasty, gastric bypass) are the only procedures that provide marked and sustained weight reduction in morbidly obese patients, leading to improvements in associated metabolic disorders, especially type 2 DM ($P < 0.001$), and a more favorable long-term prognosis, including a reduction in total mortality (adjusted hazard ratio, 0.71; $P = 0.01$).⁴⁵ However, considering the risk/benefit ratio of bariatric surgery, it may not yet be considered an early option in the management of the abdominally obese patient.

CONCLUSIONS

The management of obesity, including excess VAT, requires a multidisciplinary approach with dietary and lifestyle interventions combined with pharmacologic agents, if necessary. As obesity is now recognized as a chronic disease, treatment results should be sustained over the long term. Realistic goals should be proposed to obese patients. To this end, a 5% to 10% reduction in initial body weight may be sufficient to induce a 25% to 30% reduction in VAT among high-risk abdominally obese patients, an important factor in explaining why moderate weight loss improves the metabolic profile of most patients with metabolic syndrome, type 2 DM, and high CVD risk. Pharmacologic treatment combined with diet and exercise is likely the best approach to help patients reach this target. The future of antiobesity drug therapy will likely comprise the use of agents capable of reducing not only VAT but also adiposopathy. This may be a new and exciting research area and perhaps a promising approach in the early management of abdominal obesity.

KEY POINT

A 5% to 10% reduction in initial body weight may be sufficient to induce a 25% to 30% reduction in VAT among high-risk abdominally obese patients.

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