Management of overweight and obesity in patients with cardiovascular disease

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Abstract

Overweight and obesity affect around half of the UK population, and are a serious public health problem. Obesity is associated with hypertension, dyslipidaemia, type 2 diabetes and a sedentary lifestyle, and has been shown to be an independent risk factor for development of cardiovascular disease. There are characteristic structural changes of the heart and vasculature in obesity. There is strong evidence that even modest weight reduction lowers cardiovascular risk. Dietary intervention, lifestyle advice and increased exercise are the initial strategy, but selected patients will require adjunctive treatment with anti-obesity drugs. In the absence of contraindications, orlistat is appropriate to use in obese patients with established cardiovascular disease, though sibutramine use is contraindicated in this population. Surgical intervention, such as gastric restrictive procedures, may be needed in severe obesity but there is a high complication rate among the morbidly obese and particularly in those who are also diabetic.

Key words: overweight, obesity, cardiovascular disease, anti-obesity drugs, orlistat, sibutramine, surgical management.

Introduction

Obesity is a chronic condition characterised by an excess of body fat. Body fat is most commonly estimated using the body mass index (BMI) formula, which is the weight in kilograms divided by the square of the height in metres. While it does not distinguish fat mass from lean mass, BMI is widely used to define degrees of overweight. Overweight is defined as a BMI of 25-29.9 kg/m^2 and obesity as a BMI greater than or equal to 30 kg/m^2. Large waist circumference (>94 cm [37 inches] in males and >80 cm [32 inches] in females) reflects central adiposity and an android (apple) shape, rather than gynoid (pear) shape, is an important indicator of cardiovascular disease.[1]

Currently about half of the adult UK population is overweight or obese. In England approximately 17% of men and 21% of women are obese.[2] Both environmental and genetic factors affect the expression of obesity across the lifespan.[3] Obesity commonly develops in childhood: one in five children in England are considered overweight and one in 10 are obese. Obesity is a risk factor for several chronic diseases, including hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease, sleep apnoea, musculoskeletal problems and some cancers. The clinical manifestations of ischaemic heart disease, including angina and heart failure, are aggravated by obesity. Cardiovascular risk factors commonly cluster in patients with obesity and they may have a major impact on the individual's physical, social and emotional well being.

Estimates suggest that the combined direct and indirect (represented by loss of earnings) costs of obesity in England in 1998 were £2.6 billion or 0.3% of UK Gross Domestic Product; direct costs accounted for 18% of the total.[4] The risk of death from all causes, cardiovascular disease, cancer and other diseases increases throughout the range of moderate and severe overweight for both men (figure 1) and women in all age groups.[5]

Because of the difficulties in achieving significant weight loss by diet and lifestyle changes alone, obesity is regarded as the Cinderella of coronary heart disease (CHD) risk factors.[6] However, even modest weight loss of 5-10% can reverse many of the co-morbidities and will result in significant health gains.[7] It has been estimated that each 10% reduction in weight in men leads to a 20% reduction in coronary events.[8] This article reviews the various drugs and other interventions currently available for the management of obesity.

Cardiovascular consequences of obesity

Obesity is associated with elevated blood pressure, blood lipids, lipoproteins, glucose and the development of type 2 diabetes. It is itself an independent risk factor for development of cardiovascular disease.[9] The EUROASPIRE investigators, in a study[10] of almost 5,000 records of coronary artery disease (CAD) patients throughout Europe, identified that 75% of women and 80% of men were overweight (33% and 23% respectively were obese) at six months after hospitalisation for myocardial infarction and/or revascularisation. Interestingly, advice from a nutritionist

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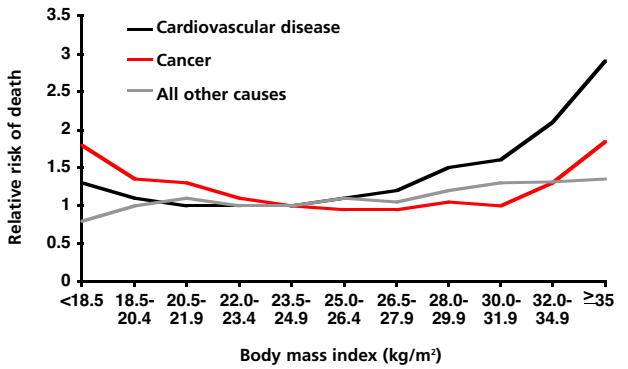
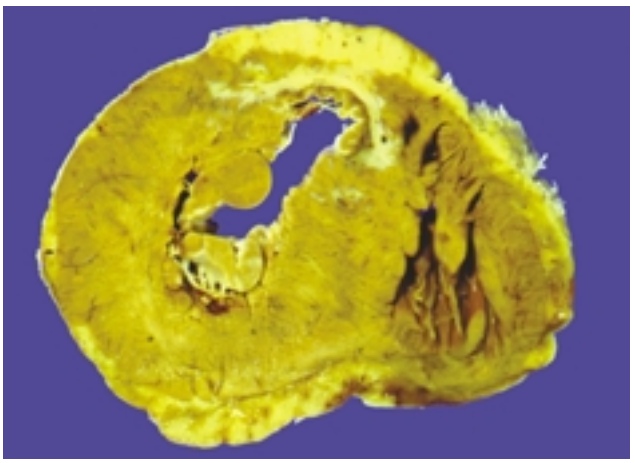
Figure 1. Multivariate relative risk of death from cardiovascular disease, cancer and all other causes among men who have never smoked and who had no history of disease at enrollment, according to body mass index. A significantly increased risk of cardiovascular death is seen at all body mass indices of more than 26.5



Adapted from: Calle EE *et al*[5]

Figure 2. Post-mortem heart (weight >800 g) of an obese male patient, showing gross hypertrophy of the left ventricle and the presence of adipocytes (fat cells) within the muscle mass



was offered to fewer than 20% of obese patients. Higher BMI is associated with elevated concentrations of C-reactive protein (CRP), suggesting a state of low-grade systemic inflammation in overweight and obese persons.[11] This effect of 'smouldering arteries' might at least partly mediate the effects of obesity on CAD, a concept which is supported by a recent study showing that obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries.[12]

Congestive heart failure (CHF) is a common complication of obesity, even in the absence of hypertension or detectable ischaemic disease. Such patients can have significantly higher left ventricular (LV) cavity size and end-systolic wall stress, and substantial weight loss can improve LV systolic function and diastolic filling, as well as improve symptoms in the morbidly obese.[13]

Cardiac chamber enlargement, left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction are also common findings in studies in the morbidly obese (figure 2); systolic dysfunction may improve following substantial weight loss. LVH markedly increases risk of sudden cardiac death. Reduced heart rate variability, which reflects autonomic imbalance and represents an independent marker of mortality (particularly sudden cardiac death), has also been shown to be present in obese patients and to improve after weight loss.[14]

A wide array of alterations in cardiac structure and function, including chamber enlargement and left ventricular heart disease, have been observed at post-mortem in morbidly obese patients (ie. those with body weight twice the ideal body weight or more) even in the absence of underlying organic heart disease or hypertension.[15] Among such patients who die prematurely, coronary atherosclerosis may not be more prevalent than might be expected for their ages.

Non-pharmacological strategies for weight loss

Is dietary intervention worthwhile? Surveys have shown that about 40% of women and 20% of men in the US are currently trying to lose weight and they are spending 33 billion dollars annually in this pursuit, yet obesity is increasing alarmingly among Americans.[16,17] While great faith is placed in dieting, with either moderate or severe caloric restriction, both are associated with increasing weight regain over time. It is estimated that some 70% of successful weight losers regain at least half of the weight lost within two years[18] and the adverse metabolic effects of some diets such as high-protein, low-carbohydrate regimens can outweigh the benefits of weight reduction. These diets are harmful in patients with CAD and should not be recommended, either to these patients or to the general public.[19] Research suggests that a combination of advice promoting a low-energy, low-fat diet (decreasing calorie intake) and increased physical activity - at least 30 minutes of moderate physical exercise on all or most days of the week, supported by behaviour therapy, is likely to be more effective than either diet or exercise advice alone.[20]

Successful weight loss is associated with improvements in the lipid profile, reductions in glucose and insulin levels, and highly significant improvements in blood pressure control[21] with less frequent increases in antihypertensive treatment. A weight reduction programme (aimed at reducing caloric intake by 1,000 calories/day) can be more effective than beta blocker treatment in lowering blood pressure.[22] The addition of exercise to diet on maintenance of body weight has been shown to produce a sustained reduction in LV mass and blood pressure.[23]

Pharmacological strategies for weight loss

The first-line strategy for weight loss is a combination of diet, exercise and behaviour modification; this should be pursued even when adjunctive therapies are used.[7] The main challenge,

Table 1. Drugs that are not appropriate for the treatment of obesity *

Amphetamine/dexamphetamine
Bulk forming agents** (eg. methyl cellulose)
Caffeine
Diethylpropion
Diuretics
Ephedrine
Fluoxetine
Human chorionic gonadotrophin (HCG)
Thyroxine #

Key: * see references 7, 24 and 25 for detailed reviews.** Although data on long-term benefits are lacking, bulking agents are licensed for use in obesity. # Thyroxine should not be prescribed for obesity in the absence of biochemically proven hypothyroidism

however, is to improve the ability to sustain, rather than to achieve, weight loss.[24] This may warrant the use of anti-obesity drugs among patients who are at medical risk from their condition. This group includes patients with a BMI of 30 kg/m^2 or more, or overweight patients (BMI=27-28 kg/m^2) with established co-morbidities, where diet and lifestyle modifications have not achieved a specified weight reduction (see below) after supervised care. There are three principal mechanisms of action of anti-obesity drugs:

- reduction of energy intake (decreasing appetite or increasing satiety)
- reduction of absorption of nutrients (eg. inhibition of gastric and pancreatic lipase)
- increase in energy expenditure; best achieved through exercise (and inappropriately with stimulants such as ephedrine or caffeine).

Drug treatment of obesity has had a chequered history.[25] Many of the older weight-reducing agents were not properly evaluated and some were withdrawn due to their adverse effects and their potential for abuse or dependency. Table 1 shows agents which are not appropriate for the treatment of obesity.

These agents (some of which have been withdrawn) are particularly unsuitable for patients with cardiovascular disease. Other drugs include fenfluramine (with its active isomer dexfenfluramine) and phentermine, both prescription medications which act principally on the hypothalamus and which were individually approved for appetite suppression. They were later available as a combination referred to as 'fen-phen' which was very widely prescribed in the US. This was found to be associated with serious side effects, including pulmonary hypertension and valvular heart disease,[26] and it has been withdrawn. Phentermine - a centrally-acting drug which has mild stimulant properties and also has some unpleasant amphetamine-like CNS side effects - is still available for short-term use in the US[27] but its European licence has been withdrawn. Metformin and acarbose have proven useful in the management of obese patients with type 2 diabetes but they have no proven efficacy for the indication of obesity alone and are not licensed for this use as a primary indication.[7]

There are currently two drugs, orlistat and sibutramine, licensed for the treatment of obesity in the UK and both have had appraisals from the National Institute for Clinical Excellence (NICE) (http://www.nice.org.uk).

Orlistat

Orlistat[24,28] is a potent and selective inhibitor of pancreatic lipase, the enzyme involved in triglyceride hydrolysis. Absorption of fat into the intestinal tract is thus prevented. Some 30% of this fat passes straight through the bowel and is excreted in the faeces. As orlistat is not absorbed systemically, its side effects are mainly restricted to the gastrointestinal tract. These are not uncommon, primarily during the first three weeks of treatment, but are likely to occur if the drug is taken with a meal which is high in fat. This may have the incidental benefit of encouraging patients to modify their fat intake and, thus, their dietary behaviour. Adverse effects include oily spotting, flatus with discharge, oily stools and faecal urgency. Orlistat does not interact with digoxin but the INR should be monitored when it is taken in association with warfarin.

Orlistat was introduced in 1999 for treatment of obese patients with a BMI greater than or equal to 30 or a BMI greater than or equal to 28 with associated risk factors (eg. diabetes, hypertension) who have been shown previously to produce a weight loss of at least 2.5 kg over four consecutive weeks. Orlistat should be taken with a mildly hypocaloric diet, with approximately 30% of calories in the form of fat (just under 39% of food energy is derived from total fat in the UK). The recommended dose is orlistat 120 mg taken at meal times (three times daily). Treatment should be discontinued after 12 weeks if patients are unable to lose at least 5% of their body weight. As there are no published safety/efficacy data beyond two years, the duration of treatment should not exceed this period. Large trials have shown that orlistat can induce one-year weight loss of 3 to 4 kg in excess of placebo.[28] As well as promoting clinically significant weight loss over a two-year period, orlistat-treated patients experience half as much weight regain compared to placebo over this same period.[29]

There are no outcome studies with orlistat in cardiovascular disease, but published data show significantly greater improvements in total cholesterol, low-density lipoprotein (LDL) cholesterol, LDL/high-density lipoprotein cholesterol ratio and in the concentrations of glucose and insulin with drug treatment versus placebo. Orlistat has been associated with clinically significant reductions in both diastolic and systolic blood pressure, with a pooled analysis showing reductions in systolic blood pressure compared to placebo of -10.9 vs -5.1 mmHg, respectively; $p<0.05$.[30] Orlistat was also associated with a significant reduction in waistline circumference compared to placebo (7.3 cm vs 4.5 cm respectively). A recent study[31] assessing the effect of weight loss on coronary risk reduction in high-risk obese patients concluded that orlistat-induced weight loss was associated with an

improvement in coronary risk profile. Published data therefore support the use of orlistat in selected overweight patients who have established cardiovascular disease or who are at high risk of it.

Sibutramine

Sibutramine[25,27,32] acts as a reuptake inhibitor for noradrenaline, serotonin and dopamine (to a lesser degree). It was initially developed as a potential antidepressant and resembles, in some of its properties, the established antidepressant venlafaxine. But it has also been show to promote satiety and weight reduction. It may also have mild thermogenic effects (increasing energy expenditure).

Sibutramine became available in the UK in 2001 and is licensed for use as an adjunct to diet in individuals with a BMI of 30 kg/m^2 or more, or with a BMI of 27 kg/m^2 with other obesity-associated risk factors such as diabetes or high cholesterol. The starting dose is sibutramine 10 mg once daily; this can be increased to 15 mg if there is less than 2 kg weight loss after four weeks. Treatment should be discontinued if the weight loss stabilises at less than 5% of the initial weight, or if weight loss is less than 5% of initial weight after three months, or if the patient regains 3 kg or more. The maximum treatment period is one year. In the recent Sibutramine Trial of Obesity Reduction and Maintenance (STORM),[33] sustained weight loss was achieved in most patients who were selected as having achieved more than 5% weight loss after six months, who continued therapy for two years. Benefits were seen in the lipid profile, as they were in a further study[34] of obese white and African American patients with hypertension controlled with a calcium antagonist with or without a thiazide diuretic. The study also demonstrated improvements in waist circumference and quality of life measures. Sibutramine has also been shown to induce decreases in glycosylated haemoglobin in obese patients with type 2 diabetes.[35]

The drug has the potential to interact with psychotropic agents, such as certain antidepressants, as well as drugs which affect the cytochrome P450 system and agents which raise blood pressure or heart rate. Side effects associated with sibutramine include anxiety, dry mouth, insomnia and constipation. Sibutramine can also raise blood pressure by an average of 2 mmHg[27] and cause increases in heart rate of 3-7 beats/min.[32] According to current advice, blood pressure and pulse should be monitored every two weeks for three months, monthly for 4-6 months and regularly thereafter. Because of its potential haemodynamic effects, sibutramine is contraindicated in patients with known coronary artery disease, congestive heart failure, tachycardia, peripheral occlusive vascular disease, arrhythmia, cerebrovascular disease and uncontrolled hypertension (for other contraindications see official prescribing information), all of which occur commonly in overweight and obese patients.

Surgical intervention

Surgical intervention is normally considered only in people with morbid obesity (BMI > 40 kg/m^2).[36] In general the weight loss associated with surgery is greater and more sustained than that achieved by non-surgical interventions. Techniques include jejunoileal bypass, vertical banded gastroplasty and gastric bypass. However, surgery is associated with complications and with a higher risk of premature death. Surgical intervention is gaining popularity in the US, where there were some 40 000 operations during the year 2000. The estimated cost for each gastric restrictive procedure is $20 000 (£14 200).[37] In one series, obesity was not associated with excess mortality in the absence of diabetes but morbid obesity was associated with increased mortality risk in both diabetic and non-diabetic patients.[38]

Key messages

- Overweight and obesity are both increasing dramatically in the UK
- Dietary intervention, lifestyle advice and increased exercise are the initial strategies for weight management
- Anti-obesity drugs may be required as adjunctive therapy when other interventions fail
- In the absence of contraindications, orlistat is suitable for treatment of obesity in patients with cardiovascular disease
- Sibutramine is an effective agent for weight loss but should not be used in cardiovascular patients
- Surgical intervention using gastric restriction may be required in some obese patients, but this has a high complication rate in the morbidly obese

Discussion

Detailed advice on the essential requirements for the management of a weight loss programme is readily accessible,[7,25,36,39,40] even if adherence to it is less widespread. Overweight patients with co-existent cardiovascular disease represent a particularly high-risk population who require aggressive management. Behavioural, diet, exercise and drug treatments have all been shown to be effective to some extent in treating obesity in adults, especially when two or more approaches are used in combination. Maintenance interventions involving continued therapist contact are necessary to sustain weight loss. Obese patients are ideally managed in primary care but those who are refractory to treatment for their weight or control of their risk factors require referral to secondary care specialist clinics for multidisciplinary management.

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