



# Weight management

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## Summary

**Obesity treatment is effective and moderate weight losses can be maintained for 4–5 years. Even small weight losses are effective in preventing diabetes, improving the control of diabetes and improving the cardiovascular risk profile. They also improve mobility, sleep apnoea and general well-being. There is a place for pharmacotherapy but drugs must be used in conjunction with a behavioural change (lifestyle) program. Pharmacotherapy (currently orlistat and sibutramine are available) used for 2–4 years can help to maintain weight loss, but the ideal duration of such therapy is uncertain. When pharmacotherapy is ceased some weight will be regained. This regain generally results in the weight increasing to the weight that would have been achieved by effective lifestyle programs. Other therapies such as very low calorie diets and obesity surgery also produce long-term successful weight loss.**

Key words: obesity, orlistat, sibutramine.

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## Introduction

In the six years since an article on 'Obesity management' appeared in *Australian Prescriber*, a great deal has changed. Obesity is now recognised as a major health and social issue. The importance of obesity in the production of disease is acknowledged in the technical report of the World Health Organization (WHO)<sup>1</sup> and the more recent clinical practice guidelines produced by the National Health and Medical Research Council.<sup>2,3</sup> An important advance is the recognition that small weight losses (5 kg or so) can have major effects on cardiovascular risk factors and the incidence of diabetes. In addition, there are more effective weight management programs, and a greater understanding of many aspects of obesity (including genes and obesity, the effects of obesity and the role of adipose tissue).

## Aetiology

For obesity to occur there must be either an increase in energy intake over our body's needs, a decrease in energy expenditure,

or both. In Australia there is an abundance of relatively cheap food and there is a decline in exercise and the activity of daily living (due to increased use of technology, 'less time', safety fears and changes to our living environment). Genetic causes are very rare.

## Adipose tissue

Adipose tissue is now known to have many functions other than energy (triglyceride) storage. It is an active endocrine organ<sup>4</sup> secreting leptin, adiponectin and resistin among other hormones. Most of these (with the exception of adiponectin) increase as the adipose tissue mass increases. The major site of secretion (with the exception of leptin) is the visceral or abdominal adipose tissue.

In humans leptin appears to have a role in protection from starvation, but the role of resistin is being debated. Adiponectin is an 'insulin sensitising' hormone and its absence may be important in the production of diabetes mellitus. Certainly people with genetic defects of adiponectin synthesis develop diabetes.

Adipose tissue also produces cytokines and pro-inflammatory factors that may contribute to atherosclerosis and vascular disease. A reduction in adipose tissue should be a major aim in our management of cardiovascular disease. The benefit of weight loss and maintenance therefore needs to be emphasised.

## Prevalence of obesity

The recent AUSDIAB study<sup>5</sup> found that approximately 20% of Australian adults were obese (BMI\* greater than 30), with slightly more women than men being obese. Two in three Australian adult males are overweight or obese, as are approximately 50% of females. In children the prevalence of overweight and obesity has doubled over the last 10–15 years, so now 5–6% are obese and 14–18% overweight.<sup>6</sup>

The increase in prevalence is worldwide and because of increasing obesity we may for the first time for a thousand years be facing a decrease in our life expectancy.<sup>7</sup>

## Risks associated with obesity

Obesity increases mortality and is associated with both metabolic disease (diabetes, hypertension, dyslipidaemia and coronary heart disease) and mechanical disease (osteoarthritis and obstructive sleep apnoea). We now know that obesity is a risk factor for certain cancers (breast, uterus, prostate, bowel, kidney and pancreas).

\* Body mass index: weight (kg)/height (m)<sup>2</sup>

While there are no good studies of the effect of intentional weight loss on mortality, an early study gave encouraging results.<sup>8</sup> A number of long-term trials are now studying the effect of 'lifestyle modification' programs, with or without pharmacotherapy. Minor weight losses can have major effects on fertility and such weight loss improves the effectiveness of *in vitro* fertilisation programs.

## Assessment of obesity

The BMI remains the simplest clinical measure of adiposity, although it has limitations at the extremes of age and in very muscular patients. There is now an international standard of BMI for age, for use in children and adolescents. There is considerable discussion about whether the BMI cutpoints for overweight and obesity used for Caucasians are appropriate for those of Asian origin or Indigenous Australians as there is some evidence that they may have a greater risk of disease at lower BMIs.<sup>9</sup> The WHO has produced a series of cutpoints<sup>10</sup> to help with this conundrum, but whether they need lower BMIs needs to be determined in a definitive study.

What is not in dispute is the need to measure central (abdominal or visceral) adiposity in clinical assessment. Abdominal adiposity is strongly associated with metabolic disease (which includes type 2 diabetes, dyslipidaemia, hypertension and cardiovascular disease) and the simplest measure of it is the waist (really abdominal) circumference. Men at high risk have waists measuring more than 102 cm and women at high risk have waistlines greater than 88 cm. Risk increases at waists of 94 cm in men and 80 cm in women. There is also accumulating evidence that these measurements are too great for Asians, so measures of 90 cm for men and 80 cm for women have been suggested as markers of high risk. Other measures of central adiposity include the waist:hip ratio, but there is argument about whether this ratio is the best assessment for epidemiological studies.

## Weight management strategies

It is important to spend time with the patient and to approach the issue of weight holistically. Several things need to be emphasised at the outset:

- current management strategies are effective and it has been possible to maintain weight losses for four years (or even longer with surgery)
- modest weight losses of the order of 5–10% of body weight produce significant benefit with cardiovascular risk reduction, control of diabetes, improvements in sleep apnoea and in mobility, increased fertility and improved quality of life
- relatively small weight losses can reduce the incidence of diabetes in those at high risk.

A behaviour change program, to alter eating patterns and increase activity, is the basis on which all weight loss and

maintenance therapies are built. A daily reduction in energy intake of 500–600 kcal aids weight loss (one calorie is equal to 4.18 joules). This can be achieved by reducing intake, preferably by reducing saturated fat while increasing the intake of fibre and carbohydrates with a low glycaemic index (GI). Protein intake may also be increased if desired. Those who maintain weight loss over the long term do so with a reduction in fat intake. Other diets such as the low GI diet and the low carbohydrate-high protein diet (e.g. Atkins, Zone) are certainly effective, but mainly appear to work by increasing satiety and/or reducing intake. The CSIRO Total Wellbeing diet combines an increase in protein with lower carbohydrate intake. The diet prescribed for weight loss should be acceptable to the patient, based on their habitual type of diet and, with a number of small changes, resulting in a reduced energy intake.

Activity should be increased. This can start with strategies to increase incidental activity (daily activities such as walking up stairs, to the railway station or to work) but can include a specific exercise program. The use of tools such as a pedometer may help and certainly it appears that prescribing exercise is important.

When behaviour changes are suggested it is important to follow up that they have been implemented and to then make further small changes or investigate why there are difficulties with the prescribed changes. Simultaneously, consider the patient's habits and any individual problems that may be contributing to the patient's weight problem. Proper medical management of problems, such as reduced mobility due to arthritis, and sleep apnoea, must be included in any 'lifestyle intervention' program.

Despite the ingrained pessimism in the Australian medical community these programs are effective. Several lifestyle interventions have been found to be beneficial in communities as diverse as the USA, Finland and China. It is possible to induce and maintain weight loss of the order of 4–5 kg for four years which is clinically significant. For example, it reduces the incidence of diabetes by 58% in high-risk groups.<sup>11</sup> This approach is far more effective and does not cost much more than a pharmacological approach (the use of metformin, a cheap drug) in the same groups to prevent diabetes.<sup>12</sup> The greater the weight loss, the greater the reduction in incidence of diabetes. With the addition of orlistat to a lifestyle program, the maintained weight loss is 6.7 kg at four years with a reduction in the incidence of diabetes in those at risk of 37% compared with the placebo group.<sup>13</sup> In the Diabetes Prevention Program the lifestyle intervention produced a weight loss of 4.6 kg and a reduction in incidence of diabetes of 58% compared to the control group. Comparison of these studies would suggest that a weight loss of 6.7 kg would produce a reduction of diabetes incidence of some 80% in those at high risk.

Adjunctive therapy is considered when patients with a BMI greater than 27 do not achieve weight loss with lifestyle

changes or have additional medical reasons such as diabetes, cardiovascular risk, sleep apnoea or arthritis. This includes pharmacotherapy, the use of meal replacements, very low calorie (energy) diets and surgery for obesity in those with BMI greater than 35 and comorbidities.

It is difficult to quantify the proportion of patients needing adjunctive therapy. It depends on the enthusiasm with which the lifestyle program is administered and encouraged, the degree of obesity-related complications and metabolic disease. It is likely that 25–30% of obese people may need adjunctive therapy.

## Pharmacotherapy

Currently orlistat and sibutramine are available to treat obesity. They must be used in association with a continuing weight loss and maintenance program. These drugs have different mechanisms of action, but both can add to the weight loss achieved with a lifestyle program. They also have additional benefits in cardiovascular risk reduction, the control of diabetes and other disorders.

Check weight loss in the first six weeks to three months.

Patients who lose weight early in treatment will be those who obtain long-term benefit. Weight tends to be lost in the first six months of a program and then a weight maintenance phase is entered. There is usually inexorable weight gain (1–2 kg per year) in those who are obese (and not on active treatment) so maintaining their weight is a major and continuing benefit. There are always adverse effects, but these are minimal when the drugs are used appropriately.

If no weight is lost in the first six weeks to two months of the program then the dose of the drug should be increased (sibutramine). If less than 5% of initial body weight is lost by six months then consideration should be given to stopping pharmacotherapy. At the moment it is clear that continuing therapy, once adequate weight loss has been achieved, helps maintain weight loss for 2–4 years.<sup>14,15</sup> Careful consideration should be given to withdrawing active medication after 1–4 years of therapy (if weight loss is maintained) but the patients must be supported with an ongoing lifestyle program. As the available data show that weight regain does occur, there is still debate about the correct procedure for withdrawing drug treatment. Perhaps the most pragmatic approach, after successful weight loss and maintenance for 12–24 months, is to withdraw the drugs and to observe. If weight is regained then consider reinstating drug therapy.

Sibutramine and orlistat are of use in helping obese adolescents maintain or lose weight. There are no available data about their use in children.

Another drug which has been shown to be effective is topiramate. This is effective at maintaining and producing further weight loss after treatment with very low calorie diets<sup>16</sup>, but the adverse effect profile is troublesome. A new drug,

rimonabant, a blocker of the endocannabinoid system, is being assessed in trials.

## Orlistat

Orlistat is an intestinal lipase inhibitor which acts in the gut to reduce fat absorption. The patient must eat a low fat diet, otherwise they will develop diarrhoea and/or fat leakage. The usual dose is 120 mg three times a day immediately before meals. In Australia, orlistat is available over the counter.

## Efficacy

In many clinical trials orlistat has been effective in producing extra weight loss (an extra 70–100%) over a standard lifestyle program. The weight loss is approximately 5 kg with placebo and 9.6 kg with orlistat.<sup>14</sup> Patients who lose 4–6 kg in the first three months will go on to lose more weight and can maintain this loss. Weight loss has been maintained in studies of two and four years' duration. Orlistat has been shown to be effective in general practice and in patients with diabetes.

In addition to weight loss, there are reductions in total and LDL cholesterol (particularly because of the mechanism of action), blood pressure and glycated haemoglobin.<sup>17</sup> After the initial weight loss phase, there is a 5–10% increase in HDL cholesterol. In patients with the metabolic syndrome<sup>18</sup> there is a significant reduction and improvement in all aspects of the syndrome. There is an improvement in many aspects of glucose metabolism (glucose concentrations, insulin sensitivity, hepatic glucose output) in patients taking orlistat.<sup>19</sup> This appears to be due to the mechanism of action of the drug, by reducing fat intake and the effects of lower concentrations of circulating free fatty acid on insulin resistance. In a study of patients with multiple comorbidities, no reduction in absolute five- and ten-year cardiovascular risk was found, but there were significant reductions in individual risk factors and in medication use for the associated comorbidities (diabetes, hypertension, dyslipidaemia).<sup>20</sup>

## Safety

The adverse effects of orlistat are mainly gastrointestinal and can be controlled by adhering to a low fat diet. These adverse effects can be a learning experience for the patient. If they avoid the foods associated with an episode of diarrhoea or fat leakage then they will be changing to a more appropriate, healthier diet.

The absorption of fat soluble vitamins is a concern, but in all the trials, although there is a reduction in vitamin concentrations, they remain in the normal range. If long-term use is contemplated it may be prudent to supplement these vitamins (supplement given at night before bed). There have been a few reports of idiosyncratic hypertension associated with orlistat, but this does not appear to be a major problem. It is appropriate to check the concentrations of fat soluble immunosuppressive

drugs such as cyclosporin when orlistat is used to reduce weight in patients who have had a transplant. Otherwise, there appear to be no interactions between orlistat and the major drug classes.

### **Sibutramine**

Sibutramine is both a selective serotonin reuptake inhibitor (SSRI) and a selective noradrenaline reuptake inhibitor. It has central and peripheral effects. It enhances satiety and reduces the desire to eat (the amount eaten at each meal is reduced by 10%). It also acts peripherally by preventing the usual fall in resting metabolic rate that occurs with weight loss. The initial dose is 10 mg daily. Blood pressure and pulse should be monitored. If there is not a weight loss of 1.5 kg or more in the first 4–6 weeks of treatment, the dose should be increased to 15 mg daily providing that the blood pressure is unchanged. Patients with diabetes tend to need the higher dose.

### **Efficacy**

Sibutramine has the same degree of effectiveness as orlistat in the extra weight loss it produces over the usual lifestyle program. The amount of weight loss with sibutramine treatment is approximately 10 kg (about double that obtained with placebo) and it has been shown to aid weight maintenance for up to two years.<sup>15</sup> Cardiovascular risk factors reduce in proportion to the degree of weight loss. There is an increase in HDL cholesterol (20–25%) which is independent of the degree of loss and is related to sibutramine treatment itself (those in the STORM trial who were treated with sibutramine initially and then switched to placebo also maintained an increased HDL cholesterol).<sup>15</sup> Sibutramine works in patients with diabetes, reducing the glycated haemoglobin in proportion to weight loss.<sup>21</sup>

### **Safety**

The adverse reactions include dry mouth, tiredness and some gastrointestinal effects. The selective noradrenaline reuptake inhibitor effect can increase the pulse rate (usually 2–3 beats per minute), and some patients may experience palpitations. With weight loss blood pressure does reduce, but the reduction is probably not in proportion to the degree of weight loss. Monitor the blood pressure as some patients may have a small rise in pressure. While sibutramine currently should not be used in those with cardiovascular disease or hypertension, a trial is investigating the effects of weight loss with a lifestyle program and sibutramine on cardiovascular outcomes.

There is a theoretical risk of serotonin syndrome. There is not yet evidence that this is a problem at therapeutic doses, but sibutramine should not be used in conjunction with antidepressants, particularly other SSRIs and monoamine oxidase inhibitors.

## **Very low calorie diets and meal replacements**

These strategies can be effective in producing and maintaining weight loss.<sup>22,23,24</sup> Meal replacements, used consistently for a few months and then intermittently, can produce and maintain weight loss for more than four years, with associated reductions in risk factors. Very low calorie diets are also effective. They may be used to initiate weight loss (a defined management protocol is necessary) and then pharmacotherapy can assist in maintaining the loss.

### **Obesity (bariatric) surgery**

Surgery is the most effective treatment for obesity. The results of the Swedish Obese Study<sup>25</sup> and from units in other parts of the world<sup>26</sup> have shown that significant weight loss (greater than 20 kg) can be produced and maintained. Any surgical procedure for obesity, to be effective long term, must be coupled with an ongoing weight loss and maintenance (lifestyle) program. Such a combined approach (appropriate patient selection, then surgery plus ongoing weight maintenance program) is essential for efficacy. The newer techniques, particularly with the inflatable gastric band, are much less invasive (performed laparoscopically), and gastric banding is easily reversible.

### **Prevention**

It is better to prevent obesity than to treat it. As well as individuals being educated about, and changing, their eating, activity and habits, it is essential that the community and government at all levels investigate ways of changing our environment so it becomes easier to maintain a healthy weight.

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*Professor Caterson has consulted with several other pharmaceutical companies, and acted on advisory boards as well as for government. He holds no shares in any pharmaceutical company.*

### Self-test questions

*The following statements are either true or false (answers on page 55)*

5. Sibutramine should not be used in patients with hypertension.
6. There is unlikely to be a long-term benefit for obese patients if they do not lose weight during the first three months of drug therapy.

### Abnormal Laboratory Results

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