

6 NON-CONVENTIONAL WEIGHT-MANAGEMENT STRATEGIES

For the majority of overweight and obese children and adolescents, management will involve the conventional strategies of dietary modification, increased physical activity, reduced sedentary behaviours, behaviour modification, and involvement of the family in the process of change (see Chapter 5). For many children, the goal of weight maintenance will, with continuing height growth, be sufficient (see Chapter 2).

With extreme degrees of obesity, however, conventional management may not be acceptable since even the best possible results will not reduce body weight to near the normal range. Extreme degrees of obesity may be associated with significant and even life-threatening co-morbidities that are known to respond to weight loss. It may not be possible to introduce physical activity and other behaviour-modification strategies until the child or adolescent has lost enough weight to achieve a degree of mobility. The most extreme cases of childhood and adolescent obesity may be associated with genetic abnormalities (for example, Prader-Willi syndrome and leptin deficiency) or physical abnormality (for example, hypothalamic obesity and craniopharyngioma) that render standard weight management ineffective.

This chapter discusses very low energy diets, a variety of pharmacotherapies, and bariatric surgery. Most of these non-conventional weight-management strategies should only be pursued in tertiary institutions with specialist obesity services, where appropriate assessment, therapy planning and multi-disciplinary support are available.

6.1 VERY LOW ENERGY DIETS

Very low energy diets have been recorded as used in children and adolescents for three decades (Figueroa-Colon et al. 1993; Stallings et al. 1988a and 1988b; Archibald et al. 1983; Brown et al. 1983; Dietz & Schoeller 1982; Merritt et al. 1981). Earlier studies were all inpatient and were very short term, with an emphasis on biochemical and metabolic effects, although weight loss was the primary outcome measure. The initiation of similar but longer term diets was generally as an inpatient, then with outpatient follow-up. Overall, the studies do not provide much information on the nature or degree of additional interventions such as exercise programs or behavioural modification. Further, the numbers are small, the selection criteria are vague, and most of the studies are uncontrolled. As late as 2000, Sothorn et al., which has reported on protein-sparing modified fasts in children for over 20 years, reported on a study with no controls and no adjustment of BMI for age. The evidence provided must therefore be considered limited.

6.1.1 Composition

Unlike interventions in adults, most very low energy diets in children have been protein-sparing modified fasts (PSMFs) (Figueroa-Colon et al. 1993; Stallings et al. 1988a and 1988b; Dietz & Schoeller 1982), although one group reported on a non-

food based very low energy diet, Optifast (Brown et al. 1983). In PSMFs, lean animal protein is the main food item, calculated as between 1.5 and 2.5 grams per kilogram of ideal body weight per day, depending on the study. The addition of vegetables is allowed in some studies, and water and non-caloric drinks are the only beverages allowed. Vitamin and mineral supplementation is included to ensure adequate adolescent requirements.

6.1.2 The risk of negative nitrogen balance

Dietz and Schoeller reported a 'modified' PSMF using 1.5 grams of protein base with either 1 gram of glucose per kilogram of ideal body weight per day or the isocaloric amount of fat. The study design was four weeks cross-over with a wash-out, and the addition of carbohydrate produced a 60 per cent mean reduction in the negativity of nitrogen balance. There was a wide variation in nitrogen balance, with most subjects reaching and maintaining negative status.

6.1.3 Age of subjects

The subjects in all the studies mentioned were generally aged 12 years or more, although the youngest in the Figueroa-Colon et al. study was 7.5 years. This study defined an enrolment criterion as 140 per cent or more of ideal body weight. The mean enrolment percentage of ideal body weight in the various studies varied from 140 to over 200 per cent, although included in these figures are adolescents with weights closer to 120 per cent of IBW.

6.1.4 Duration of therapy

The longest reported use of a non-food very low energy diet in adolescents was the 1983 uncontrolled descriptive study by Brown et al. Optifast, a fully supplemented liquid meal based on casein and egg-white solids, was used. This provided 1.5 grams of protein per kilogram of ideal body weight per day and a total of 500-700 kilocalories. Stallings et al. and Figueroa-Colon et al. reported shorter VLED times of approximately three months but provided follow-up data to 12 and 14 months respectively. In the Stallings et al. study, treatment was initiated in hospital and then there was two-weekly follow-up for the duration of the PSMF but none after, until the 12-month re-assessment. This, too, was an uncontrolled descriptive study. Figueroa-Colon et al. assessed the efficacy of a completely outpatient-initiated and outpatient-maintained therapy. Visits were weekly for the duration of the PSMF and then monthly thereafter, when on a standard hypocaloric diet (20 per cent protein, 30 per cent fat and 50 per cent carbohydrate). The PSMF group was compared with children who were placed on a standard hypocaloric diet for the 14 months of the study, which was not randomised.

6.1.5 Initial weight loss results

Weight loss, at least in the short term, is impressive. In the Optifast study the majority of weight was lost in the first five weeks (a mean of 15 kilograms), when subjects were hospitalised, but weight loss continued over the entire 20 weeks of therapy (a mean total loss of 30 kilograms). In Stallings's group a similar pattern, albeit with shorter hospitalisation, was observed, with a mean fall in ideal body weight of 25 per cent at the end of the PSMF; this fall was maintained at 12 months on a standard

hypocaloric diet. The ideal body weight is the percentage of measured weight over the matching weight percentile for the subject's current height percentile. For the Figueroa-Colon et al. subjects, figures, provided as mean percentage of change in ideal body weight at 2.5, 5.5 and 14.5 months, were – 29.5, – 32.2, – 23.3 for the PSMF group and – 13.8, – 17.5 and – 20.3 for the hypocaloric diet group. Beneficial effects were noted for cardiovascular risk factors when assessed in those subjects on VLEDs, but, since these were not compared with results obtained from standard hypocaloric diet therapy it is not possible to say whether VLEDs offer an additional benefit for cardiovascular risk. A controlled six-month school-based study has been reported (Figueroa-Colon et al. 1996): weight loss using the PSMF at 2 grams per kilogram of ideal body weight per day followed by a standard hypocaloric diet was 25 per cent of ideal body weight compared with 0.3 per cent in the controls.

6.1.6 Adverse effects

In two studies reporting at least 12 months' follow-up, the attrition rate was similar, at 30 per cent. Early falls in serum proteins, including albumen and retinol-binding protein, occur (Merritt et al. 1981) but not out of the normal range. Lean body mass falls over the long term but no more than expected for the loss of body fat and towards predicted levels (Stalling et al. 1988b; Brown et al. 1983). Growth velocity has been reported as either unchanged or slowed during VLED therapy (Figueroa-Colon et al. 1993), reverting when calories were liberalised. In the case of Figueroa-Colon et al., this seems to be a real effect because growth velocity was reported as Z scores, which became negative during the VLED period. This was also the study with the youngest children. Orthostatic hypotension, transient alopecia, lymphopaenia, hyperuricaemia, and cardiac arrhythmias have all been reported. Diarrhoea, halitosis, muscle cramps, fatigue, headache (Figueroa-Colon et al. 1996), and gall stones are other potential adverse effects.

6.1.7 Summary

Very low energy diets—whether they involve normal food items or non-food substitutes—produce rapid weight loss in adolescents. This may be a true benefit when there is significant medical co-morbidity. The longer term benefits are less clear because of the lack of controlled trials comparing VLEDs and standard hypocaloric diets. Any VLED therapy in adolescents should be initiated in a specialist referral centre, and consideration should be given to initial hospitalisation if there are associated medical conditions that may be better dealt with in the hospital environment. There is evidence both for and against hospitalisation providing an added weight-loss advantage. In relation to the duration of therapy, there are limited safety data to 20 weeks for food-substitute VLEDs and 12-week data for PSMFs. There is no evidence to support the use of VLEDs in children. If their use in a child were to be considered in a specialist paediatric centre, it should be treated as an individual clinical trial.

Evidence-based statement	Evidence level
Very low energy diets (VLED) produce a rapid weight loss over a short period in adolescents.	III-2

Recommendation: level B

- VLED therapy in adolescents should be undertaken only by specialist obesity-management teams. VLED therapy is never indicated for children.

Evidence-based statement**Evidence level**

The evidence that very low energy diets produce any long-term weight-loss benefit is unclear.

IV

Recommendation: level C

- After cessation of a very low energy diet, there should be a continuing weight-management plan.

6.2 PHARMACOTHERAPY FOR OBESITY IN CHILDHOOD AND ADOLESCENCE

There have been no randomised placebo-controlled trials in children of anti-obesity agents that satisfy the one-year criterion used for this document. Because of ethical constraints, such studies are unlikely ever to be carried out in children, either with current drugs or with those that become available in the future. There is a case to be made for trials in obese adolescents, especially those with co-morbidity and no growth potential. Mazindol, an agent no longer in use, has been studied in the short term, but the studies (Komorowski et al. 1982; Golebiowska et al. 1981) offer nothing for the development of these guidelines and are not discussed here.

6.2.1 Centrally acting agents

Phentermine

A number of studies of children using phentermine were reported in the 1960s (Rauh & Lipp 1968; Lorber 1966; Spranger 1965). In the two placebo-controlled trials available in English (those of Rauh & Lipp and Lorber) the age range was 3 to 19 years. The protocol in the Lorber study does not comply with current research guidelines. At the end of three months, 90 per cent of subjects taking phentermine, 82 per cent of those taking amphetamine and 46 per cent of those on a placebo were recorded as having lost weight; the absolute mean losses for the first two groups were 1.4 and 1.7 kilograms respectively, while the third group recorded nil weight loss. Severe insomnia was the only reported adverse effect for phentermine. Rauh and Lipp's study of chlorphentermine in 28 adolescent females, who were provided with no lifestyle instruction, reported a mean loss for phentermine of 6.7 kilograms compared with a gain of 0.5 kilograms for placebo.

Diethylpropion

Diethylpropion has been studied in two randomised controlled trials in children and adolescents (Stewart et al. 1970; Andelman et al. 1967). The duration of therapy was variable, up to 12 weeks, and there was minimal dietary instruction. In the short term diethylpropion produced a mean weight loss of up to 5 kilograms; this compares with the controls, whose mean weight remained basically unchanged.

Fenfluramine

Two controlled studies have reported on fenfluramine use in children and adolescents (Malecka-Tendera et al. 1996; Bacon & Lowrey 1967). Therapy was combined with a standard hypocaloric diet. The mean weight loss for fenfluramine was significantly more than that for placebo in only one of the trials. A less well designed, but longer, study in adolescents aged between 11 and 17 years was reported by Pedrinola et al. (1994). In the fenfluramine group there was a continuous fall in overweight in the 12 months, from 154 per cent of ideal body weight to 123.4 per cent; the placebo group lost 7 per cent. Adverse effects were minimal, occurred mainly at initiation, and responded to dose reduction. A double-blind placebo-controlled cross-over trial for fenfluramine has also been reported in subjects with Prader-Willi syndrome (Selikowitz et al. 1990). The maximum amount of weight lost was 6 kilograms. Food-related and aggressive behaviour showed significant improvement while subjects were taking the active drug.

The drug is no longer available.

Sibutramine

The anti-obesity agent sibutramine has some similarities in action to dexfenfluramine. There are no studies in subjects aged less than 18 years. The STORM Study Group reported its findings on the effect of sibutramine after weight loss (James et al. 2000). The weight loss was achieved by the prescription of a 600-kilocalorie deficit diet and 10 milligrams of sibutramine daily. Subjects who continued with sibutramine to 24 months were able to sustain the weight loss. Use of sibutramine in this manner seems potentially efficacious for adolescents with significant obesity.

Statement

There is no evidence that sibutramine has a role in the management of adolescent obesity.

Recommendation: level D

- Because of lack of data, including data on short- and long-term harm, sibutramine should be used in obese adolescents with co-morbidity only in a specialist centre and only when there is a reasonable expectation of benefit over risk.

Research recommendation

- Long-term use of sibutramine in adolescents with obesity associated with significant co-morbidity should be trialled.

6.2.2 Agents that interfere with nutrient absorption

Orlistat is a unique anti-obesity agent in that it is negligibly absorbed and its mode of action is inhibition of fat absorption. There are now published data for two years of its use in adults. Orlistat has a clear advantage over placebo in weight-loss trials in adults, with the achievement and maintenance of about a 10 per cent body-weight loss and a concomitant improvement in obesity-related co-morbidity. There are no randomised controlled trials of orlistat in adolescents or children. Use of the agent in children, who could not understand the delayed gastrointestinal consequences of excess fat ingestion and who are actively growing, is not indicated. Ongoing randomised trials in adolescents are currently being conducted (J Yanowski, US National Institutes of Health, pers. comm., 24 April 2001).

The results of a three-month non-controlled study of orlistat in adolescents have recently been published; they show good tolerability and weight loss (McDuffie et al. 2002). This was an open-label trial in 20 adolescents (10 males) with a mean age of 14.2 years, with a mean BMI of 43.8, and with obesity-related co-morbidity. Seventeen of the subjects completed three months of treatment, which included diet, exercise and behavioural therapy. The mean SD losses for BMI and percentage of body fat were -1.44 ± 1.78 and -4.6 ± 4.2 respectively. Fasting cholesterol and LDL cholesterol were significantly lower when compared with baseline, and insulin sensitivity improved significantly. The only side effects were gastrointestinal, but these were mild and decreased with time. Three subjects required vitamin D supplementation.

Evidence-based statement	Evidence level
Short-term uncontrolled trial data suggest that orlistat may assist with weight loss in obese adolescents.	IV
Recommendation: level C	
<ul style="list-style-type: none"> Because of limited data, including data on short- and long-term harm, orlistat should be used in obese adolescents with co-morbidity only in a specialist centre and only when there is a reasonable expectation of benefit over risk. 	
Research recommendation	
<ul style="list-style-type: none"> Well-designed clinical trials of the use of orlistat in obese adolescents with obesity-related co-morbidity are needed. 	

6.3 OTHER PHARMACOTHERAPEUTIC AGENTS

6.3.1 Ephedrine/caffeine

Ephedrine/caffeine has recently been reported in a 20-week randomised double-blind placebo-controlled pilot study in obese adolescents (Molnar et al. 2000). There were small but significant falls in adiposity measures in the active treatment group. There are no grounds on which to prescribe this medication for children or adolescents.

6.3.2 Octreotide

Cranial damage can induce an intractable form of obesity (see Section 3.11). Hyperinsulinaemia is considered to have an important aetiological role in this condition. In 1999 Lustig et al. reported on eight children who developed intractable obesity after therapy for leukaemia or solid brain tumours and who were treated with octreotide, a long-acting somatostatin receptor that reduces pancreatic beta-cell insulin secretion (Lamberts et al. 1996; Hsu et al. 1991). Lustig et al.'s was an open-label study lasting six months. After the six months of octreotide therapy, peak insulin responses had decreased by two-thirds and glucose tolerance had improved. Compared with an initial six months of observation, where the mean weight gain was 6.0 ± 0.7 kilograms, the weight change at the end of six months of octreotide was -4.8 ± 1.8 kilograms. Most patients had transient gastrointestinal effects, and four had asymptomatic gall bladder sludge or stones, which resolved after the cessation of therapy. Lustig's group went on to a double-blind placebo-controlled trial with 18 subjects aged between 8 and 18 years; to date, this has been reported in abstract form only (Lustig et al. 2001). The study confirmed the findings of the open-label trial, showed that the gall bladder sludge and stones resolved with ursodiol, and that quality of life, as measured by validated questionnaire, improved. Longer term trials in specialist centres are needed, but such treatment may improve morbidity and wellbeing in patients with hypothalamic obesity.

6.3.3 Leptin

There is a case report of a 9-year-old leptin-deficient girl who was treated with recombinant leptin (Farooqi et al. 1999). The leptin was injected subcutaneously daily, with no other intervention. In the first 12 months of therapy, the girl's weight loss was 1 kilogram a month—almost exclusively loss of fat mass.

6.3.4 Metformin

Metformin has been shown to enhance muscle and adipocyte insulin receptor number and affinity, increase insulin receptor tyrosine kinase activity, and augment GLUT4 transporter number and activity (Cusi et al. 1996). Recently, it has also been shown to improve fatty liver in obese leptin-deficient mice, an effect attributed to a reduction in hepatic tumour necrosis factor (Lin et al. 2000). The evidence that metformin has a place in weight management is not clear, and there is limited information in relation to children and adolescents.

The findings of DeFronzo et al. (1995) and the UK Prospective Diabetes Study Group (1998) confirm the validity of metformin as the initial drug of choice in obese type 2 diabetes in adults: it is the only oral agent that did not cause weight gain. Metformin also has a specific role for ovulation induction in polycystic ovarian syndrome. When the drug is combined with a standard low-energy diet, there is a greater reduction in BMI and body weight than occurs with placebo and diet in both women with the syndrome and obese women without it, suggesting that the drug has an independent effect on body weight (Pasquali et al. 2000). Further, results from the Biguanides and Prevention of Risks of Obesity (BIGPRO) Trial suggest that metformin affects several cardiovascular risk factors in non-diabetic subjects with central adiposity (Fontbonne et al. 1996).

A recent study specifically considered the use of metformin in non-diabetic obese hyperinsulinaemic adolescents in a randomised double-blind placebo-controlled trial (Freemark & Bursey 2001). Over six months the metformin group significantly reduced BMI (no other weight-management intervention was provided) and there were slight but significant falls in fasting glucose and insulin.

Metformin would be the initial choice for oral therapy both in obese adolescents with type 2 diabetes (based on adult studies) and in obese adolescents with polycystic ovarian syndrome, particularly where regulation of the menstrual cycle is desired, in conjunction with lifestyle management.

Evidence-based statement	Evidence level
Metformin appears to have a potential role in therapy in obese non-diabetic hyperinsulinaemic adolescents.	III-3
Recommendation: level C	
<ul style="list-style-type: none"> Consider metformin therapy in the obese adolescent with significant hyperinsulinaemia and who has a family history of diabetes. 	

6.3.5 Growth hormone

Obese children have normal to accelerated height growth, generally normal insulin-like growth factor 1, but decreased growth hormone secretion on a number of dynamic tests (Argente et al. 1997; Loche et al. 1987). It is uncertain what role these functional abnormalities play in obesity. Kamel et al. (2000b) reported on seven obese pre-pubertal boys who received growth hormone for six months with no lifestyle intervention: there was a reduction in body fat and no deterioration in glucose tolerance.

6.4 BARIATRIC SURGERY

Older adolescents may appear as individual patients in studies of bariatric surgery in adults. The only studies considered here, however, are those where the study subjects are exclusively children and adolescents.

The early bariatric procedure was jejunoileal bypass. There are a number of reports of this in adolescents (Silber et al. 1986; Organ et al. 1984; Randolph et al. 1974; White et al. 1974). Since jejunoileal bypass is no longer a recommended procedure for morbid obesity, these studies are not dealt with in detail here. Not all subjects had major weight loss; in those whom the studies identified as successful, the mean weight loss was 50 kilograms, with reported losses up to 90 kilograms. There was a high prevalence of post-operative morbidity. Nearly one-third of subjects had a re-anastomosis.

6.4.1 Current surgical procedures

Bariatric surgical procedures now target the stomach, with either a reduction in pouch volume (vertical gastric or external banding) or bypass using the Roux-en-Y procedure. Studies in children and adolescents are confined to gastric bypass (Strauss et al. 2001; Anderson et al. 1980; Soper 1975) and vertical banded gastroplasty (Greenstein & Rabner 1995). There are no published studies or case reports on lap banding in adolescents. The Soper and Anderson et al. studies are from the same institution (a highly specialised referral centre), with a single surgeon performing the majority of procedures. Recently Vandenplas et al. (1999) reported on a six-month study of five adolescents (aged between 11 and 17 years) with intra-gastric balloons. A non-significant trend to a lowering of BMI was noted at three months only.

6.4.2 Guidelines for surgical intervention

There are no published guidelines for weight-loss surgery in children and adolescents. Anderson used the criteria of Printen and Mason (1973)—100 per cent above ideal body weight, good health except for obesity-related disorders, and the potential for normal physical activity. Similar criteria were used by Strauss et al. (2001). In total, for all studies there were 69 subjects and 11 of these had Prader-Willi syndrome (all in the Anderson et al. study). Ages ranged from 13 to 20 years, with a mean of 17 years. The main pre-operative co-morbidities described were obstructive sleep apnoea, hypertension, and severe psychological disturbance.

Subjects lost a mean of 60 per cent of their weight above ideal body weight, with genetically normal females and Prader-Willi subjects losing less. Weight loss tended to plateau at 15 to 20 months, and some females experienced significant regain with pregnancy.

Three deaths were reported. One was in the immediate post-operative period, one was three years later and while on the 'Dr Atkins' diet, and one was a Prader-Willi patient in whom weight gain continued and revision of surgery was declined. Post-operative morbidity was high and included infection, poor wound healing, symptomatic cholelithiasis, and micronutrient deficiencies. One subject required total parenteral nutrition for protein-calorie malnutrition. No satisfactory height data are provided, although it is assumed that most subjects were past their active growth phase.

Evidence-based statement	Evidence level
<p>There is evidence that gastric restrictive or gastric bypass surgery induces a weight loss in adolescents, with a reduction in obesity-related co-morbidity that is comparable to that found in adult studies. The overall numbers are low, however; and long-term follow-up data are limited. Not every subject experiences significant weight loss, and there are no good data to suggest who will be successful. Post—operative morbidity is common.</p>	IV

Recommendation: level C

- Bariatric surgery might be considered as the last possible option in a severely obese adolescent with obesity-related co-morbidity. Such a procedure should be undertaken only in an experienced surgical centre after extensive consultation, lengthy education of the patient and their family, and full psychological assessment. Continuing post-operative care in an experienced weight-management service would be mandatory.
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