Aggressive Therapy for Childhood and Adolescent Obesity

Jack A Yanovski

Unit on Growth and Obesity, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA

For obese children and adolescents, treatments to minimize future weight gain and induce weight loss are necessary to prevent the development of long-term complications of obesity. Programs prescribing moderate energy restriction, increased physical activity, and decreased sedentary behavior should always be the first line of approach for the overweight child (1). At least one such program has shown long-term efficacy of weight control in a substantial portion of the 6- to 12-year-old children participating (2,3). Unfortunately, many children and adolescents—especially those with severe obesity—may not respond to such programs. As a result, various, more aggressive therapeutic approaches have been proposed for obese children who have failed conservative treatment. Aggressive approaches include restriction of energy intake below 1,000 kcal/d, pharmacotherapy, and bariatric surgery. In this paper I will review the limited data on these aggressive treatment regimens in childhood obesity and detail their potential benefits and risks.

INDICATIONS AND CONSIDERATIONS FOR AGGRESSIVE TREATMENT OF PEDIATRIC OBESITY

In general, only those children and adolescents who have a body mass index (BMI) greater than the 95th centile for age and sex and who also have developed a demonstrable obesity-related comorbid condition that may be remediable by weight reduction should be considered for aggressive treatment. All overweight children and adolescents should have their BMI plotted on a sex-appropriate BMI chart (Figs. 1 and 2) to determine the severity of their obesity. Many complications of obesity are observable during childhood, including dyslipidemia (high total cholesterol, low-density lipoprotein cholesterol and triglycerides, and reduced high-density lipoprotein cholesterol), disorders of glucose metabolism ranging from hyperinsulinemia through glucose intolerance to frank type 2 diabetes, hepatic steatosis, systolic and diastolic hypertension, pseudotumor cerebri, sleep apnea, and orthopedic complications such as Blount disease and slipped capital femoral epiphysis (4).
2 to 20 years: Boys
Body mass index-for-age percentiles

FIG. 1. Body mass index for boys 2 to 20 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion.
FIG. 2. Body mass index for girls 2 to 20 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion.
Most obesity specialists recommend that the intensity of the proposed treatment match the severity of the obesity. For this severity-intensity matching, many investigators describe pediatric body weight relative to the subject’s “ideal body weight” (IBW), defined as the 50th centile weight-for-height for a child of the same age and sex. Any child who is more than 120% of IBW (equivalent to a BMI greater than the 95th centile) may be a candidate for a standard program of behavior modification, a 500-kcal/d-deficit diet, and increased activity. Very-low-energy diet programs are generally employed only for those more than 140% of IBW (5), and bariatric surgery is usually restricted only to those weighing at least double their IBW (6).

All aggressive treatments for pediatric obesity—whether they involve dietary restriction, pharmacotherapy, or surgery—should be considered as adjuncts to behavioral treatment designed to improve diet, increase physical activity, and decrease inactivity. Because the best results seem to be found in programs using multidisciplinary teams not readily available to the individual practitioner, aggressive treatments for pediatric obesity should whenever possible be carried out in specialized centers that have experience with such treatments.

Finally, as many of the aggressive treatment regimens for obesity are considered investigational when used in children, it may be advisable to obtain written informed consent from parents before initiating such treatments.

AGGRESSIVE REGIMENS TO RESTRICT INTAKE

The conventional pediatric dietary prescription for weight loss typically aims to reduce intake by approximately 500 to 700 kcal/d (to induce a 0.5-kg weight loss each week). Except for the youngest children, this generally results in total energy intakes of more than 1,000 kcal/d. More restrictive diet prescriptions are termed very-low-energy diets. The most common version of the very-low-energy diet is the proteinsparing modified fast (PSMF). Currently employed PSMF regimens supply a daily intake of between 600 and 800 kcal and 1.5 to 2.5 g of high-quality protein per kilogram of ideal body weight. They also usually restrict carbohydrate intake to 20 to 40 g/d. Such formulations do not cause cardiac arrhythmias or sudden death, as was observed in the 1970s, when liquid protein diets containing only hydrolyzed collagen as a protein source were used (7,8). Many PSMF programs use readily available lean meats, poultry, and fish as protein sources (9), although commercially available formula diets consumed as liquids may induce a PSMF. Patients using a PSMF are recommended to take a daily vitamin and mineral supplement and consume more than 1,500 ml of free water daily. In most programs, a PSMF is prescribed for no longer than 12 weeks, and is conducted under medical supervision. Figueroa-Colon et al. (5) found that 12 third to fifth graders weighing more than 140% of IBW enrolled in a comprehensive 6-month school-based program that included a 10-week PSMF lost 5.6 ± 7.6 kg, versus a weight gain of +2.8 ± 3.1 kg in seven untreated control children. Some uncontrolled trials suggest at least some weight loss can be found up to 1 year after a PSMF. Stallings et al. (10) treated 17 obese adolescents with a PSMF for 3 months, along with diet and activity counseling, and found that at follow-up 1 year later, 48% had maintained at least some weight loss. Soothers et al. (9) reported
that among 87 children weighing more than 120% of IBW who remained enrolled in a 1-year multidisciplinary weight reduction program that included 10 weeks of PSMF, an exercise program, and behavior modification sessions, weight was 8.4 kg less after 1 year of treatment than at baseline. However, no information about dropouts was presented, and no control groups using a higher-energy diet were studied. Some investigators have employed PSMFs for longer periods. Suskind et al. (11) reported results from 50 obese children and adolescents 7 to 17 years of age who enrolled in a 10-week nutrition, activity, and behavior modification education program plus a PSMF. They allowed those who were still more than 150% of IBW to continue, taking the PSMF for as long as 30 weeks. Whenever they stopped the PSMF, all subjects were offered a 1,200-kcal/d balanced diet maintenance program consisting of weekly exercise sessions and bimonthly educational programs. Fifteen subjects (30%) took the PSMF for more than 15 weeks. While 80% completed the 10-week program, only 60% were reported to have entered the weight maintenance program, and only 40% were reported as having a 26-week follow-up. However, those subjects with the 26-week follow-up reduced their body weight by approximately 9 kg and had improvements in plasma lipids. Whether these results are better than those achievable with conventional dietary interventions has not been proven.

In children aged 7 to 17 years randomized to participate in a PSMF (600 to 800 kcal/d) or a hypocaloric balanced diet (800 to 1,000 kcal/d) plus a behavior modification program for 10 weeks, who were then placed on a 1,000- to 1,200-kcal/d balanced diet, Figueroa-Colon et al. (12) reported greater weight losses in children taking the PSMF (−11.2 versus −5.1 kg, \( p < 0.01 \)) at the 10-week time point. However, follow-up 1 year later revealed similar mean weights in both groups (12), suggesting no long-lasting benefit of the PSMF relative to a balanced hypocaloric diet.

The potential risks of PSMF regimens include cholelithiasis, hyperuricemia (13), decreases in serum proteins including transferrin, retinol-binding protein, and complement \( \beta_2 \)C (14), orthostatic hypotension, halitosis, and diarrhea (15). Serious complications in patients treated with modern PSMFs appear to be rare.

In sum, PSMF programs seem to be reasonably safe when carried out under medical supervision, and produce more rapid weight losses in the short term than conventional diets. However, they have not been shown to offer significant improvements in long-term outcome compared with less restrictive diets offered in the context of a comprehensive program. Although selected patients may benefit from a PSMF, particularly when rapid short-term weight loss is desirable (e.g., those who must lose weight before a surgical procedure can be performed, or who have life-threatening complications of obesity), it remains unclear whether programs employing a PSMF are better at inducing the long-lasting significant weight changes desired for treatment of pediatric obesity than long-term programs using moderate energy restriction.

PHARMACOTHERAPY

Because obesity is now believed to be a chronic disease best treated using a long-term medical treatment model (16), drugs that might be prescribed for long periods have
been investigated. Although adverse effects have led to some anorectic agents being withdrawn from use, in the interests of completeness I will review in the following section all drug treatments for obesity that have been studied in children or adolescents, as identified by a MEDLINE search and manual review of published reports, even if the drug is no longer available (Table 1). As will be seen, there have been no long-term (≥1 year), randomized, double-blind, placebo-controlled trials in which the efficacy of drug treatment has been compared against that of a program including diet, exercise, and behavior modification.

**Drugs Reducing Energy Intake**

A few pediatric studies have examined the efficacy of drugs that reduce food intake by decreasing appetite or increasing satiety.

**Fenfluramine** decreases appetite by stimulating the release of both serotonin and dopamine from nerve terminals and selectively inhibiting their reuptake, and, particularly when combined with phentermine, appeared to decrease body weight in adults (16,17). One randomized, double-blind, placebo-controlled trial of the effects of fenfluramine on the weight of 5- to 18-year-old children found no difference in short-term weight loss between those taking placebo and those taking fenfluramine (18). Similar results were reported in a nonrandomized study with an untreated control group (19). Pedrinola et al. (20) performed a nonrandomized, placebo-controlled trial of fenfluramine in 11- to 17-year-old overweight Brazilian children who were given a minimal diet and exercise intervention (visits every 2 months). When examined after 12 months, the fenfluramine-treated children who remained in the study decreased BMI by −5.1 kg/m², whereas in placebo-treated children the change in BMI was −1.3 kg/m² (p < 0.05) (20). Because this study was not reported as randomized or double blind, did not report results from a substantial portion of enrolled subjects, and did not include a significant behavioral modification, diet, or exercise program, it is not possible to interpret the results as indicating an advantage of fenfluramine treatment over conventional programs. The potential risks of fenfluramine treatment led to its being withdrawn from use by its manufacturer in 1998, when cardiac valvopathies similar to those seen in the carcinoid syndrome were found to follow its use (21,22).

**Phentermine** is an orally active, DEA schedule C-IV-controlled substance that affects appetite by increasing the release of norepinephrine and dopamine from nerve terminals and inhibiting their reuptake. Two studies lasting 4 weeks using phentermine resin, 5 to 15 mg, versus placebo have reached contradictory conclusions about its efficacy in children and adolescents (23,24). Rauh and Lipp (25) compared weight change in 28 adolescent girls enrolled in a randomized controlled trial to receive either chlorphentermine 65 mg/d or placebo. Subjects were seen every 2 weeks, but not given an exercise or diet intervention. During the 12-week trial, those receiving chlorphentermine lost significantly more weight (−6.7 kg) than those taking placebo (+0.55 kg). Longer-term follow-up was not performed.

**Diethylpropion** and **mazindol** are other orally active DEA schedule C-IV controlled substances, with a mechanism of action similar to that of phentermine that
have been evaluated as anorectic agents in children and adolescents. Two randomized controlled trials (26,27) studied diethylpropion hydrochloride 65 mg/d given for 8 to 12 weeks, in conjunction with minimal dietary interventions, and found that subjects taking diethylpropion lost 2 to 5 kg more than those taking placebo. Longer-term follow-up was not done. Short-term studies with mazindol suggest similar short-term improvements in weight loss (28–30).

The side effect profiles of phentermine, diethylpropion, and mazindol in adults include insomnia, restlessness, euphoria, palpitations, hypertension, cardiac arrhythmias, dizziness, blurred vision, and ocular irritation. Sympathomimetic agents such as phentermine, mazindol, or diethylpropion cannot be used concurrently with monoamine oxidase inhibitors.

Sibutramine, an inhibitor of the synaptic reuptake of norepinephrine, serotonin, and dopamine, has been found in adults to decrease weight in 6-month to 1-year randomized, double-blind, placebo-controlled studies (31). Side effects have included increases in blood pressure and pulse, which are usually mild but which may be substantial in some patients. Other adverse reactions include headache, insomnia, anxiety, nervousness, depression, somnolence or drowsiness, edema, palpitations, diaphoresis, xerostomia, constipation, dizziness, paresthesias, mydriasis, and nausea. Sibutramine cannot be given in conjunction with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors. Clinical trials evaluating the safety and efficacy of sibutramine in adolescents are ongoing, but no data from children or adolescents are currently available.

Drugs Reducing Absorption of Nutrients

There have been no published randomized, placebo-controlled trials of drugs that affect absorption of nutrients from the gastrointestinal tract in children or adolescents.

Orlistat, an inhibitor of gastrointestinal lipases, has been shown in placebo-controlled trials to have modest efficacy in adults for periods as long as 2 years (32–34). A 3-month open-label trial of orlistat reporting a 4.6% decrease in body fat in a small number of very overweight adolescents (initial BMI 43.8 ± 12.4 kg/m²) has been published in abstract form (35). Side effects include decreases in fat-soluble vitamin levels (primarily vitamin D), flatulence with discharge, fecal urgency, fecal incontinence, steatorrhea, oily spotting, and increased frequency of defecation. These side effects are usually mild to moderate, and generally decrease in frequency with continued treatment. Placebo-controlled, randomized, double-blind clinical trials evaluating the safety and efficacy of orlistat in adolescents are ongoing.

Other Drugs

Leptin

Leptin is a hormone secreted by adipocytes, the level of which, under nonfasted conditions, reflects total body lipid content (36,37). Serum leptin concentrations fall precipitously during fasting, and it appears likely that its intended function is primarily
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Subjects</th>
<th>Treatment duration</th>
<th>Nondrug intervention</th>
<th>Study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacon and Lowrey, 1967 (18)</td>
<td>RCT</td>
<td>71% F, 5–17 y, &gt;97th weight centile</td>
<td>1 month, then</td>
<td>1,000–1,200 kcal/d diet prescription</td>
<td>d,l-fenfluramine 10–20 mg bid or tid, Placebo</td>
</tr>
<tr>
<td>Pedrinola et al., 1994 (20)</td>
<td>Not clear if randomized but had placebo control group</td>
<td>55% F Brazilian children 11–17 y, 120% of IBW</td>
<td>12 months</td>
<td>800–1,000 kcal/d diet, instructed to increase activity, Visits q2 mo</td>
<td>d,l-fenfluramine 30–60 mg bid, Placebo</td>
</tr>
<tr>
<td>Malecka-Tendera et al., 1996 (19)</td>
<td>Non-randomized untreated control group</td>
<td>71% F Polish children 16 ± 2 y, unresponsive to outpatient program</td>
<td>6 weeks</td>
<td>Inpatient admission for 3 weeks 600 kcal/d diet, outpatient for 3 weeks 800 kcal/d diet</td>
<td>D,L-fenfluramine 15 mg bid, No medication</td>
</tr>
<tr>
<td>Komorowski et al., 1982 (30)</td>
<td>RCT</td>
<td>43% F Polish children age 9–15 y</td>
<td>8 weeks</td>
<td>Low-calorie diet</td>
<td>Mazindol 1 mg/d, Placebo</td>
</tr>
<tr>
<td>Golebiowska et al., 1981 (28,29)</td>
<td>Not clear if randomized but had placebo control group</td>
<td>44% F Polish children age 9–16y</td>
<td>8 weeks</td>
<td>2-week residential 1,600–1,800 kcal/d, with supervised activity, then outpatient None, visits q2 weeks</td>
<td>Mazindol 1 mg/d, Placebo</td>
</tr>
<tr>
<td>Rauh and Lipp, 1968 (25)</td>
<td>RCT with last observation carried forward</td>
<td>100% F Tanner IV or V pubertal development age 10–19 y</td>
<td>12 weeks</td>
<td>Chlorphenter mine 65 mg/d</td>
<td>Placebo</td>
</tr>
<tr>
<td>Von Spranger, 1965 (23)</td>
<td>Placebo controlled, unclear if randomized</td>
<td>Children, 5–15 y</td>
<td>1 month</td>
<td>Diet prescription, 1 visit</td>
<td>Phentermine 5–15 mg/d, Placebo</td>
</tr>
<tr>
<td>Lorber 1966 (24)</td>
<td>RCT</td>
<td>62% F age 3–15 y, &gt;120% of IBW</td>
<td>1 month, then</td>
<td>No snacks between meals, no sweets, to canned fruits</td>
<td>Phentermine 15 mg/d, Amphetamine resinate 12.5 mg/d, Placebo</td>
</tr>
<tr>
<td>No. of</td>
<td>Final number of</td>
<td>BMI (kg/m²) or % IBW or weight (kg) at baseline</td>
<td>Change in weight (kg) or BMI (kg/m²) at endpoint</td>
<td>% Reduction in weight at endpoint</td>
<td>Side effects in treated subjects</td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>subjects</td>
<td>completing study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5 (50%)</td>
<td>NR</td>
<td>−3.0 kg</td>
<td>NR</td>
<td>Weakness, dizziness, fainting, disorientation</td>
</tr>
<tr>
<td>10</td>
<td>9 (90%)</td>
<td>NR</td>
<td>−1.5 kg</td>
<td>NR</td>
<td>Drowsiness (18%), dry mouth, nausea, diarrhea</td>
</tr>
<tr>
<td>90</td>
<td>68 (76%)</td>
<td>29 ± 5 kg/m² (154 ± 24%)</td>
<td>−5.1 kg/m²</td>
<td>NR</td>
<td>Dry mouth (58%), sleep disorders (21%)</td>
</tr>
<tr>
<td>40</td>
<td>17 (42%)</td>
<td>30 ± 4 kg/m² (161 ± 28%)</td>
<td>−1.3 kg/m²</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>19 (100%)</td>
<td>31 ± 5 kg/m² 85 ± 19 kg</td>
<td>−3.9 kg/m²</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>19 (100%)</td>
<td>34 ± 12 kg/m² 80 ± 19 kg</td>
<td>−5.7 kg/m²</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8 (100%)</td>
<td>66 ± 10 kg</td>
<td>−5.7 ± 1.5 kg</td>
<td>−11.7%*</td>
<td>Palpitations (9.5%), dry mouth (33%), skin eruption (4.7%)</td>
</tr>
<tr>
<td>6</td>
<td>6 (100%)</td>
<td>59 ± 8 kg</td>
<td>−3.0 ± 2.2 kg</td>
<td>−6.9%</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>21 (100%)</td>
<td>71 kg</td>
<td>−5.4 kg</td>
<td>−7.6%*</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20 (100%)</td>
<td>90 kg</td>
<td>−3.4 kg</td>
<td>−4.9%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>13 (93%)</td>
<td>95 kg</td>
<td>−6.7 kg**</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>10 (77%)</td>
<td>96 kg</td>
<td>+0.55 kg</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>41 (100%)</td>
<td>23 kg</td>
<td>−3.5 ± 1.5 kg</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>31 (100%)</td>
<td>21 kg</td>
<td>−19 ± 1.8 kg</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20 (100%)</td>
<td>24 kg</td>
<td>−1.9 ± 1.4 kg</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>84 total</td>
<td>24 kg</td>
<td>−3.4 kg</td>
<td>NR</td>
<td>Insomnia, Irritability</td>
</tr>
<tr>
<td>22</td>
<td>22 total</td>
<td>22 kg</td>
<td>−2.2 kg</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Subjects</th>
<th>Treatment duration</th>
<th>Nondrug intervention</th>
<th>Study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart et al., 1970 (27)</td>
<td>RT with last observation carried forward</td>
<td>58% F age 5–16 y &gt;97th centile for weight</td>
<td>8 weeks, then crossover for 8 weeks</td>
<td>1,200 kcal/d diet prescription</td>
<td>Diethylpropion 75 mg qd Placebo</td>
</tr>
<tr>
<td>Andelman et al., 1967 (26)</td>
<td>RCT</td>
<td>84% F age 12–18 y &gt;120% of IBW</td>
<td>11 weeks</td>
<td>No snacks between meals</td>
<td>Diethylpropion 75 mg qd Placebo</td>
</tr>
<tr>
<td>Lustig et al., 1999 (45)</td>
<td>Open label</td>
<td>56% F children 8–18 y with hypothalamic obesity</td>
<td>6 months</td>
<td>Dietary counseling</td>
<td>Octreotide 5 μg/kg/d + tid</td>
</tr>
<tr>
<td>Lustig et al., 2001 (46)</td>
<td>RCT</td>
<td>39% F children 10–18 y hypothalamic obesity</td>
<td>6 months</td>
<td>NR</td>
<td>Octreotide 5–15 μg/kg/d + tid Placebo</td>
</tr>
<tr>
<td>McCann et al., 2000 (35)</td>
<td>Open label</td>
<td>50% F black and white children 12–17 y</td>
<td>3 months</td>
<td>Psycho educational program; 12 weekly 500 kcal/d deficit diet</td>
<td>Orlistat 120 mg tid</td>
</tr>
<tr>
<td>Farooqi et al., 1999 (40)</td>
<td>Open label</td>
<td>100% F leptin deficient children 12–17 y</td>
<td>12 months</td>
<td>None</td>
<td>Recombinant leptin</td>
</tr>
<tr>
<td>Lutjens and Smith 1977 (53)</td>
<td>Open label</td>
<td>8–14 y children</td>
<td>3 months</td>
<td>Diet prescription</td>
<td>Metformin 500 mg tid Diet alone</td>
</tr>
<tr>
<td>Lustig et al., 1999 (54)</td>
<td>Open label</td>
<td>100% F 1.3–17 y Obese adolescents M and F</td>
<td>28 weeks</td>
<td>Diet prescription None reported</td>
<td>Metformin 500 mg tid Metformin 500 bid Placebo</td>
</tr>
<tr>
<td>Freemark and Bursey, 2000 (55)</td>
<td>RCT</td>
<td>8–18 y with hypothalamic obesity</td>
<td>6 months</td>
<td>No snacks between meals</td>
<td>Diethylpropion 75 mg qd Placebo</td>
</tr>
</tbody>
</table>

Abbreviations: RCT, randomized, double-blind, placebo-controlled trial; NR, not reported. For crossover studies, results from first treatment period are reported.

* $p < 0.05$.

** $p < 0.01$ vs. control.
<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Final number of subjects (%) completing study</th>
<th>BMI (kg/m²) or % IBW or weight (kg) at baseline</th>
<th>Change in weight (kg) or BMI (kg/m²) at endpoint</th>
<th>% Reduction in weight at endpoint</th>
<th>Side effects in treated subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>−2.1 kg*</td>
<td>NR</td>
<td>Headache, abdominal pain, increased activity</td>
</tr>
<tr>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td>+0.36</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>37 (73%)</td>
<td>154%</td>
<td>−5.1 kg</td>
<td>−16.9%</td>
<td>Drowsiness, jitteriness, nervousness, insomnia, dry mouth, irritability, headache</td>
</tr>
<tr>
<td>46</td>
<td>10 (22%)</td>
<td>154%</td>
<td>+0.3 kg</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>8 (89%)</td>
<td>36 ± 2 kg/m²</td>
<td>−4.8 ± 1.8 kg</td>
<td>−4.6%</td>
<td>Edema (11%) abdominal discomfort, flatulence, or loose stools (78%), increased thyroid hormone requirements (67%), gall bladder sludging (44%)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>All subjects</td>
<td>+1.6 ± 0.6 kg**</td>
<td>NR</td>
<td>Diarrhea (100%), glucose intolerance (22%), bile sludging/gall stones (44%)</td>
</tr>
<tr>
<td></td>
<td>99 ± 6 kg</td>
<td>+9.2 ± 1.5 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 ± 1.3 kg/m²</td>
<td>+2.2 ± 0.5 kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>17 (85%)</td>
<td>44 ± 12 kg/m²</td>
<td>−2.9 ± 4.8 kg</td>
<td>−2.6%</td>
<td>Low vitamin D (3/20); oily stools (20/20)</td>
</tr>
<tr>
<td></td>
<td>1 (100%)</td>
<td>48 kg/m²</td>
<td>−16.4 kg</td>
<td>−17.4%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>10 ± 6 kg</td>
<td></td>
<td>−10.1 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>9 (100%)</td>
<td>29 ± 4 kg/m²</td>
<td>−4.8 ± 1.6 kg/m²</td>
<td>−16 ± 6%**</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>9 (100%)</td>
<td>68 ± 19 kg/m²</td>
<td>−10.9 ± 4.1 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 ± 4 kg/m²</td>
<td>+0.3 ± 1 kg/m²</td>
<td>+1.6 ± 3.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>9 (100%)</td>
<td>70 ± 20 kg</td>
<td>+1.1 ± 2.5 kg**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (100%)</td>
<td>39 ± 2 kg/m²</td>
<td>−1.2 ± 0.7 kg/m²</td>
<td>−3.4 ± 1.9%</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>15 (94%)</td>
<td>116 ± 9 kg</td>
<td>−0.5 kg/m²</td>
<td>−1.3%*</td>
<td>Intermittent nausea (6%)</td>
</tr>
<tr>
<td>16</td>
<td>14 (88%)</td>
<td>42 ± 4 kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 ± 5 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td>Abdominal discomfort (19%); exacerbation of migraine (6%)</td>
</tr>
</tbody>
</table>
as a peripheral signal to the hypothalamus of an inadequate food intake (38) rather than as a satiety signal. A few children have been identified who are unable to make functional leptin protein (39). Such individuals have severe early-onset obesity. Treatment of a leptin-deficient girl with recombinant leptin has been reported to induce a dramatic effect on body weight (40). Over a 12-month treatment period she lost weight at a rate of approximately 1 to 2 kg a month, with a total weight loss of 16.4 kg, of which 95% was due to reduction in adipose tissue mass. Considerably less dramatic changes in body weight have been observed in leptin-sufficient adults treated with differing regimens of recombinant leptin (41,42). It remains unknown whether leptin treatment of obese children or adolescents who do not have mutations in the leptin gene will be of benefit.

Octreotide

Among its many effects, the somatostatin receptor agonist octreotide can suppress pancreatic secretion of insulin by inhibiting G0 protein effects on voltage-dependent calcium channels. Octreotide has therefore been evaluated for its ability to affect body weight in patients believed to have obesity resulting from primary hyperinsulinemia, particularly those who have suffered cranial insults. In rodents and humans, damage to the ventromedial hypothalamus (VMH) can cause considerable obesity and significant hyperinsulinemia. Although the observed hyperinsulinemia may in part be a response to insulin resistance induced by weight gain, there is evidence that VMH damage induces neurally mediated hyperinsulinemia, acting through the autonomic supply to the pancreas. In rats, hyperinsulinemia is found shortly after surgical disruption of the VMH, and either vagotomy or denervation of the pancreas can prevent the weight gain that follows such hypothalamic lesions (43,44).

Lustig et al. (45) proposed the hypothesis that neurally mediated hyperinsulinemia could be one of the primary stimuli for overeating in children who have sustained damage in the region of the hypothalamus. To test this hypothesis, they examined the effects of suppressing insulin secretion with octreotide in a pilot study of children who had intractable obesity following intracranial treatment for brain tumors or leukemia (45). Whereas before starting treatment, these children were gaining an average of 6.0 ± 0.7 kg every 6 months, while taking octreotide they lost 4.8 ± 1.8 kg over a 6-month interval. Because these data were collected in an open-label fashion, the true magnitude of the benefit cannot be determined. A recent report in abstract form of a 6-month randomized controlled trial using octreotide or placebo in 18 children with hypothalamic obesity found weight stabilization in treated subjects (+1.6 ± 0.6 kg in 6 months), in contrast to significant weight gains (+9.2 ± 1.5 kg in 6 months) in those receiving placebo (46). Because somatostatin has many actions, it is also unknown whether the effects of octreotide at the pancreatic level are the explanation for these children’s weight loss.

There are many known complications of octreotide treatment, such as pain at injection sites, gallstones, diarrhea, abdominal pain, nausea, vitamin B-12 deficiency (47), hypothyroidism, suppression of growth hormone secretion, frank type 1 diabetes, and abnormalities of cardiac function. As a result, larger studies with longer
treatment duration are needed to determine whether this drug provides sufficient benefit for children with intractable obesity related to hypothalamic injury. Octreotide offers a novel approach to the treatment of hypothalamic obesity in children and continues to be studied in placebo controlled trials.

**Metformin**

Metformin is a drug that inhibits hepatic glucose production and is used for the treatment of type 2 diabetes. It not only improves hyperglycemic indices, but also decreases weight gain and promotes weight loss in adults (48–52). It has been used in a limited number of school-aged children and adolescents with obesity. In one open-label study, metformin 500 mg three times daily was given to nine obese children 8 to 14 years of age, who were also given dietary instruction (53). There was an impressive reduction in weight over a 3-month period of $-10.9 \pm 4.1$ kg (range $-4.0$ to $-15.0$ kg). More recently, two small studies of metformin have been reported. Lustig et al. (54) treated eight obese, hyperinsulinemic adolescent girls with open-label metformin (2,000 mg/day) for 28 weeks and reported a mean decrease in weight of $0.53 \pm 0.69$ kg per month. Freemark and Bursey randomized 29 obese adolescents with hyperinsulinemia to metformin 500 mg twice daily or placebo without any dietary treatment, and found a 1.3% decrease in BMI following use of metformin for 6 months versus a 2.3% increase in BMI for those taking placebo ($p < 0.05$) (55). Because such studies have not examined subjects in comprehensive weight management programs, it is unclear whether metformin treatment improves the outcome found with such programs.

Metformin may cause nausea, flatulence, bloating, and diarrhea at the start of treatment, and approximately 5% of adults cannot take it at any dose because of these symptoms. Vitamin B-12 deficiency has also been reported in as many as 9% of patients using metformin. The most feared complication of metformin is lactic acidosis, which is estimated to occur at a rate of 3/100,000 patient-exposure years, primarily in patients with contraindications to the use of metformin. These contraindications include renal insufficiency, defined as a serum creatinine of $\geq 124$ μmol/l in women and $\geq 133$ μmol/l in men, congestive heart failure requiring drug treatment, any cardiac or pulmonary insufficiency severe enough to result in hypoxia and reduced peripheral perfusion, liver disease, and alcohol use sufficient to cause acute hepatic toxicity. Metformin should also be withheld when patients are admitted to hospital with any severe illnesses, with any condition that may cause decreased systemic perfusion, or when the use of contrast agents is anticipated. Randomized controlled trials testing the efficacy of metformin for control of weight in children and adolescents with hyperinsulinemia are ongoing.

**Drug Treatment Summary**

At present, none of the currently approved drugs for the amelioration of obesity can be recommended for obese children and adolescents, except in the context of clinical trials. Given its efficacy (40), leptin replacement therapy for leptin-deficient children
does appear justified. It is possible that ongoing clinical trials will provide the necessary data within the next few years to support the use of pharmacotherapy for other causes of childhood obesity. Because obesity is a chronic condition that requires continuous treatment, both the immediate and long-term risks and benefits of pharmacotherapy must be carefully weighed before drugs are prescribed for obese children or adolescents.

**BARIATRIC SURGERY**

There are limited data regarding surgical procedures to induce weight loss in severely obese children and adolescents (65–62). Water-filled balloons placed within the stomach to induce a sense of fullness have recently been shown not to be effective at decreasing BMI in morbidly obese children (61). Silber et al. (60) described 11 morbidly obese adolescents who underwent jejunoileal bypass. Ten years later, they had maintained weight losses ranging from 45 to 90 kg. Unfortunately, each patient had at least one complication of the procedure. These complications included encephalopathy, cholelithiasis, nephrolithiasis, renal cortical nephropathy, hypoproteinemia, and other nutritional deficiencies. More than 25% had complications that required reversal of the operations. Other studies of jejunoileal bypass have shown similar results (59).

Because of the severity of the complications from jejunoileal bypass, this procedure is now rarely performed. Instead, the Roux-en-Y gastric bypass (RYGB) has become the most commonly performed type of bariatric surgery. RYGB involves dividing the stomach to create a small (15- to 30-ml) stomach pouch into which a segment of jejunum—around 15 to 60 cm below the ligament of Treitz—is inserted, while the proximal portion of the jejunum that drains the bypassed lower stomach and duodenum is reanastomosed 40 to 75 cm below the gastrojejunostomy (Fig. 3). In adults, rapid weight loss is usually observed, and with it improvement of comorbid conditions, including resolution of type 2 diabetes in more than 80% of cases (63) and improvements in hepatic steatosis (64). Early postoperative complications include staple line leaks, wound dehiscence, subhepatic abscess, small bowel obstruction, thrombophlebitis, and pulmonary embolus. Late postoperative complications include stomal stenosis, incisional hernia, volvulus, gastrointestinal bleeding, marginal ulcers, cholelithiasis, and nutritional deficiencies (65). The perioperative mortality and complication rates in one very large adult series were 1.5% and 8.5%, respectively (66).

Older adolescents who have undergone RYGB have been included in various case series of adults (65,67,68), but their results have not usually been reported separately. One group has reported results of obesity surgery, primarily RYGB, in genetically normal adolescents and in adolescents with the Prader–Willi syndrome, all of whom weighed more than twice their IBW (6,58). In the later, more complete report (6), 30 karyotypically normal adolescents decreased their weight from 238% of IBW before RYGB to 187% of IBW 5 years later, whereas those with Prader–Willi syndrome decreased weight from 231% of IBW to 175% of IBW 5 years later. Complications
FIG. 3. Roux-en-Y gastric bypass. First, a small stomach pouch is created by stapling or by vertical banding. This causes restriction in food intake. Next, a Y-shaped section of the small intestine is attached to the pouch to allow food to bypass the duodenum as well as the first portion of the jejunum. This causes reduced calorie and nutrient absorption. (Original drawing by David Fallang, MD.)

included wound infections and dehiscence (10%), stomal obstruction (5%), atelectasis and pneumonia (12%), subphrenic abscess (2%), and death (5%). Ten patients, four who were karyotypically normal and six with Prader–Willi syndrome (amounting to around half of their patients with Prader–Willi syndrome) required surgical revisions for failure to lose weight. Three developed incisional hernias requiring further surgery. More recently, Strauss et al. (62) reviewed a separate case series of 10 obese adolescents (BMI 52.5 \( \pm \) 10.0 kg/m\(^2\)) who underwent bariatric procedures, mostly RYGB, and were followed for a mean of 69 months (range, 8 to 144 months). After bariatric surgery, 90% had weight losses of more than 30 kg (the mean weight loss was 53.6 \( \pm \) 25.6 kg), comprising 65% of their excess body weight; patients also had improvements in comorbid conditions. Complications included iron deficiency anemia (50%), transient folate deficiency (30%), and events requiring operative interventions (40%) (cholecystectomy in 20%, small bowel obstruction in 10%, incisional hernia in 10%).

Greenstein and Rabner (69) studied the long-term effects of vertical banded gastroplasty in 18 adolescents, 14 of whom (three boys and 11 girls) were willing to be interviewed an average of 5.1 years after surgery. All but one child had a significant decrease in BMI (on average by 14.6 kg/m\(^2\)). As a group, these children lost 55.9% of their excess body weight, and 79% lost more than 25%. The major morbidity described in this case series of vertical banded gastroplasty was the development of
recurrent gastric ulceration in two patients (70). Comparison studies in adults suggest that the efficacy in terms of long-term weight reduction and improvement in quality of life following RYGB is greater than that seen with restrictive procedures such as vertical banded gastroplasty (71–74), although there are no such studies in children or adolescents.

These case series suggest that patients in the pediatric age group who undergo RYGB trade the disorders associated with obesity for lifelong medical care for nutritional deficiencies but do have large sustained weight reductions following the procedures. Although bariatric surgery is the only treatment for which there is any evidence of significant and long-lasting weight-reducing effects in severely obese adolescents, such interventions cannot be recommended for any but those at the highest risk of mortality from their obesity. We agree with Strauss et al., who concluded that "gastric bypass remains a last resort option for severely obese adolescents" (62).

SUMMARY AND CONCLUSIONS

The aggressive treatments that have been used for pediatric and adolescent obesity include very-low-energy diets, pharmacotherapy, and bariatric surgery. None of these approaches has been reported in large enough numbers of subjects who have taken part in well-designed experiments with long-term follow-up to demonstrate convincingly their true value in the treatment of pediatric obesity. As the potency of the treatment increases, so does its possible adverse consequences. Of the aggressive approaches, only in the case of bariatric surgery are there even small studies supporting its ability to induce long-lasting effects (more than 1 year) on body weight in severely obese adolescents without a defined syndrome. Leptin treatment of those rare children who have genetic mutations of the leptin gene also appears justified.

Future studies of aggressive treatments in children and adolescents should in general be carried out in large, diverse samples; be designed as randomized controlled trials; be carried out for 6 months or longer; and include a comprehensive weight management program offered to all participants. They should systematically evaluate adverse events and include follow-up of most, if not all, subjects. It would also be useful if such studies reached conclusions regarding appropriate subject selection, or offered a risk–benefit calculation so that the value of aggressive treatments for individual subjects could be judged. Studies examining prevention of weight regain after aggressive treatments are also lacking for the pediatric population. In particular, the use of pharmacotherapy for preventing weight regain in children and adolescents has received little attention. Systematic trials of the efficacy of differing bariatric surgical approaches are also lacking in children and adolescents.

The risks and benefits of aggressive weight management treatments should be carefully weighed before they are used in patients in the pediatric age group. Until further controlled trials become available, aggressive treatments for pediatric obesity should be considered only for those who have not responded to conventional weight management programs but have significant complications of their obesity. Aggressive approaches should generally be restricted to specialized centers that have
experience with those treatments and should be carried out in the context of a comprehensive weight management program.

REFERENCES


DISCUSSION

Dr. Dietz: I have a couple of comments. The claims of safety that Suskind and his coworkers made about the protein-sparing modified fast were only based on 50 patients. One of our findings that we never published was that in our inpatients who were either on the protein-modified fast—which is what I call it, because I’m not sure that it is actually protein sparing—and/or on an isocaloric, isonitrogenous diet containing carbohydrate, we regularly saw ventricular arrhythmias that disappeared when the diet was normalized. We never were able to replicate this finding when we used the diets in outpatient centers. The reason may have been that when we were studying the patients as inpatients, we had them on a very restricted diet, whereas in the outpatient situation there was more diversity. I think you were properly cautious in saying that informed consent is still required. I’m not sure that we have put the issue of cardiac arrhythmias properly to rest in this population, where the myocardium may be more sensitive.

My second comment is that a couple of months ago I calculated the cost of putting every patient in the United States with a BMI of more than 30 on drug treatment, based on the local cost of Sibutramine in Atlanta. The direct costs of obesity in the United States are known to be of the order of 50 billion dollars a year, while the cost of putting every obese person in the United States on Sibutramine worked out at about 35 billion dollars a year. This puts us in a peculiar situation—we have a problem we cannot afford to treat, and one that we cannot afford not to treat!

Dr. Campos: We heard Dr. Steinbeck say that growth requires very few calories. But we also heard Dr. Ouy and Dr. Chen say that in the developing countries, when they switch from malnutrition to obesity, there is a lack of linear growth. Furthermore, those children apparently have some form of dyslipidemia. In view of the delay in catch-up growth, the dyslipidemia, and the obesity, and also the fact that obese children enter puberty earlier, might there not be a place for thyroid hormone supplementation? It is known that the malnourished population tends to have a low T4 with a normal TSH. Although this is probably mainly an adaptive response, might it not also be a mechanism contributing to the delay in catch-up linear growth?

Dr. Yanovski: I don’t believe there is any place for thyroid hormone treatment in anyone for the treatment of obesity, except where there is clear evidence of significant hypothyroidism.

Dr. Maffei: I am concerned about the high mortality from obesity surgery. I think a 5% mortality is very high. Do you have any views about criteria for surgery other than ideal body weight?

Dr. Yanovski: The 5% mortality was from a fairly early paper. I think the mortality is lower than that in more recent series, and the laparoscopic approach decreases it even more so, though I have seen no laparoscopic series in children. Dr. Strauss, do you want to comment on this?

Dr. Strauss: I can make a quick comment on each of the aggressive treatments because we use them all in some form or other. Protein-sparing modified fast in a child of less than 14 or 15 years of age is punitive, so we only use it in selected children who demonstrated motivation and who have been in our program for at least 2 to 3 months. In that setting, where the harder changes are made first, you may have some long-term weight loss, but only one in 20 or 30 of the children we see are qualified for that diet. Even the best drug treatments only produce a 10- to 12-kg weight loss compared with placebo, and in most cases less. In children who are 100 kg overweight, this won’t do anything to reduce their morbidity, while children who need to lose 10 to 12 kg should exercise and eat properly and shouldn’t be on medicines. As far as surgery is concerned, I have only referred a handful. Generally these have had severe sleep apnea and ventricular arrhythmias and are at high medical risk. They have all been on
other types of treatment. Other children selected for surgical treatment are those with severe orthopedic problems and also the most difficult group with serious psychological disturbances—children who are missing school, who are frankly depressed, and who can’t face their peers because of their weight. Some of those did have surgery and tended to be referred through the parents, who also had the surgery. Everyone I tracked down up to 10 years later was extremely happy with the results of their surgery.

I don’t know who needs surgery. The children who you think may need to have it don’t want it, and the ones who ask for it shouldn’t have it. The published mortality figures were on some of the initial patients done in the 1960s and reported in the 1980s.

Dr. Yanovski: I believe you still need to think very hard before you decide to refer an adolescent for a gastric bypass, given the fact that you are going to be trading one set of disorders for another. Although the nutritional deficiencies are manageable, they are real and can be significant.

Dr. Uauy: In relation to the hypothalamic syndrome, the craniopharyngiomas also fit into that category. Immediately after surgery, there is usually an acute increase in weight. Is there anything that can be done before they get to be massively obese?

Dr. Yanovski: I think this may be a matter of keeping a close eye on how fast they are crossing the centiles, to decide when they are getting into trouble. In general, I think that right after surgery for craniopharyngioma the most important thing is probably to ensure adequate hormone replacement therapy with thyroid hormone and growth hormone. If in spite of that you see a rapid increase in weight, the chances are that the child is going to develop this full-blown syndrome. The question then is whether octreotide therapy is good enough to use at this point. I’m not convinced of that and I think we need some longer-term data. The side effects are real. Even though we can control gallstones with ursodeoxycholic acid, that is a complication that could lead to surgical intervention. The other side effects such as diarrhea are also major problems. Also, in any individual who does not have growth hormone deficiency and who is not being treated with growth hormone, the expectation is that the child is going to become growth hormone deficient because of the treatment. Second, the way this drug works is by inducing a relative insulinopenia in the blood. This means that at some point at least there is bound to be hyperglycemia, which could, in the long term, lead to the complications associated with diabetes—and the avoidance of diabetes is of course one of the reasons why we might want to protect these children from massive weight gain. So I think there are a lot of issues to be clarified before octreotide treatment should be used as a routine approach.

Dr. Bar-Or: Just a comment regarding craniopharyngioma. We have five or six girls who are being followed up after surgery for this condition. We have managed them quite well with a multidisciplinary behavioral approach, so at least in our hands we felt that there was no need for anything drastic. Obviously, they were getting their hormone replacement therapy, but as far as their obesity was concerned they responded quite nicely to behavioral changes.

Dr. Yanovski: I think there is no question that the first step in any individual who is overweight has to be conventional management. I am also equally convinced that there are individuals who have lost their capacity to respond to leptin who will develop significant obesity that will not be controlled by conventional approaches.

Unidentified participant: Is it better to use single therapy or a combination of treatments?

Dr. Yanovski: By the time you’ve got as far as surgery I’d be very loath to combine that with drug treatment, but conventional dietary management is certainly part of the postoperative care of anyone who has had surgery. There is significant interest in combination pharmacotherapy in any situation, and we will certainly have more information relating to Sibutramine, which seems to have more than one mechanism of action. Caffeine and ephedrine is a combination therapy that has been tried. One of the areas that would be interesting to look
at is the prevention of weight regain by pharmacotherapy after a very-low-energy diet. To the best of my knowledge that has not been studied in the pediatric population.

Unidentified participant: Are there some new drugs on the horizon?

Dr. Yanovski: I have restricted my remarks to those drugs that have had some clinical trials in pediatric populations. There are various compounds under development that may be of interest to us in the future, but I’d rather not speculate on which of these will ever get out of the drug companies’ hands and into ours.

Dr. Steinbeck: Apart from leptin, none of the drugs that have been discussed are well-targeted. That is a significant problem. Leptin works very well because it is targeted at the etiology of a particular form of obesity. Until we have drugs that are more effectively targeted, including those for hypothalamic obesity, we will continue to have the sort of results that you’ve talked about today.

Dr. Yanovski: That’s very true. One of our jobs as clinicians has to be the development of a nosology of obesity that allows us to determine which groups might respond to different therapeutic approaches.

Dr. Anantharaman: Have you studied the eating habits of these very overweight children at all? I assume that they must be consuming massive amounts of food in order to continue to gain so much weight? Is this associated with any particular eating pattern?

Dr. Yanovski: The general answer is that a fair number of these children do have evidence of binge eating, although surprisingly few will meet the criteria for the binge eating disorder. Depression is present in about a third of cases. We haven’t looked carefully at whether the night eating syndrome is present or not. There is not as much secretive eating in the younger children as you might imagine. Once they are adolescents, though, there is often a lot of the same type of disordered eating you see in adults.

Dr. Jiang: What is the compliance with a very-low-calorie diet, and is it damaging to development and growth?

Dr. Yanovski: Compliance with a very-low-calorie diet is quite variable, and children under 13 or 14 years of age don’t have the maturity to be on such a restricted diet. I wouldn’t try it unless there is a really severe medical indication. The compliance issue is certainly substantial. Various programs have insisted on ketosis and measurable ketones in the urine as a measure of compliance, and even when you do that the best programs probably get around 70% compliance at best—and that’s after everyone who does not comply has dropped out.

In terms of growth and development, there are some data from Figueroa-Colon’s paper (1) suggesting that at least over a period of a year there are no adverse consequences on growth, although short term there did appear to be a deceleration of growth velocity in the protein-sparing modified fast group. In contrast, Epstein’s studies of conventional dietary management have not shown any decrements in growth velocity and final height attainment (2).

Dr. Rusli Sjarif: Do you have any experience with aggressive treatments for obesity in children under 10 years old?

Dr. Yanovski: There are very few published trials that have included children under the age of 10. I don’t believe there are any good data that I can point to that would recommend the use of aggressive therapy in such young children. One should be very cautious in young children to avoid problems with growth and development.

REFERENCES