

Therapeutic Approach to Obesity in Children and Adolescents

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ABSTRACT

The increasing incidence of obesity and of metabolic syndrome among children and adolescents has become a problem in Turkey as in the rest of the world. Given its detrimental effects on public health and the costs of its management, prevention of obesity and its treatment in childhood has gained significance. In these respects, the prescription of minimally one hour of daily physical activity for obese children and adolescents and the maintenance of this regimen has become the first measure. The second important measure is dietary control. In special cases agents that reduce appetite or gastrointestinal absorption may be used. In cases with insulin resistance and glucose intolerance, metformine is currently being used.

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INTRODUCTION

Prevention and treatment of obesity in childhood, a condition which leads to a chain of health problems in adulthood, has gained much importance in medical practice in recent years. There are more than a billion obese people worldwide. In the USA, 12% of infants between 6 and 23 months are overweight and one third of all children experience problems of obesity. Globally the number of the obese has risen to four fold of that of the undernourished and is increasing further. Between 1963 and 2004, obesity increased from 3 to 17% among adolescents, from 4 to 19% in children of 6-11 years of age and from 5 to 14% in children 2-5 years of age. In Kayseri, Turkey, the incidence of overweight and of obesity in the age group of 6-17 years were found to be respectively

15.8% and 3.9% in boys and 15.8% and 3.4% in girls (unpublished data).

GENERAL THERAPEUTIC APPROACHES

Rationality of early treatment

As in adults, obese children and adolescents usually present with morbidity and emotional distress. The fragile disposition of the children to develop these complications necessitates prevention and early treatment. Presence of marked metabolic complications in some obese children requires early intervention.

When should intervention be initiated?

It has been shown that in obese children and adolescents with body mass index (BMI) z scores of >2, the fasting plasma concentrations of glucose, insulin,

SUPPLEMENT

triglycerides (TG), C reactive protein (CRP) and interleukin 6 (IL-6) are increased, while those of HDL-cholesterol and adiponectin are decreased. Dyslipidemia and insulin resistance have been reported in overweight children (BMI 85-95th percentile) as compared to those with BMI values <85th percentile.(2) These findings indicate the necessity of modifying the diet and lifestyle of all children with BMI values >85th percentile.

The metabolic complications of obesity surface at adolescence and early adulthood. There are four major indications to start treatment in obese children.(1, 2, 3) The first is the observation of sleep apnea and Blount's disease in toddlers and small children. The second is the laboratory findings of glucose intolerance, Type 2 diabetes mellitus (T2DM), dyslipidemia and hypertension in a prepubertal obese child. The third is excessive weight gain between the ages of 2 and 10 years, especially if there is history of obesity and/or diabetes mellitus (DM) in the parents. The fourth is the observation of early vascular lesions and atherosclerosis in children of 3-8 years of age.

An effective treatment of obesity at early ages has a greater success rate as compared to interventions in adulthood.

Which treatment should be given initially?

Lifestyle: The benefits of changing the patient's lifestyle are based on the success of dieting and exercise programs, on educating individuals and families and creating changes in behaviour and attitudes. The long term success of this treatment approach depends on continuous follow up of patients because weight gain reappears in most cases. The causes of failure should be looked for in eating disorders and psychiatric problems. The lifestyle and eating habits of the parents influence the success or failure in this respect, therefore weight reduction in the obese child has been achieved by taking the parents as the target population.

Diet: Slight calory reduction in the food intake of the obese child could be effective in weight loss, provided the child and the family are motivated, encouraged and supported correctly.(2, 3, 4, 5) The children should be made to comprehend the difference between appetite and hunger and their attention should be drawn away to topics other than those on food and eating. A reduction of 100 calories in the daily diet would correspond to gaining 5 kg less annually. Rather than fast weight losses, monthly 1-2 kg losses are considered as ideal. A 'traffic lights' diet is prepared for the family, with one portion of the Green diet, Yellow diet and Red diet containing, respectively, 0-19 g, 2-49 g and >5 g fat. While calory is restricted energy intake is increased. A high protein diet with significant calory restriction would ensure dramatic losses of weight in a short time span. Heavy calory restriction would cause an insufficient intake of vitamins, minerals and microfoods, resulting in adverse side effects like reduced bone mineralisation, fall in linear growth and menstsruation disorders. The role of the dietary macrofoods in the development and treatment of obesity is currently a subject of debate. The combination of reduced fat diets with exercise is highly effective in reducing the risks of T2DM, of glucose intolerance and of cardiovascular disease in adults. Again, diets with low carbohydrate content result in faster weight loss and reduction of the plasma triglycerides in the adult obese, as compared to the low fat diets. Similar trials of 3-month duration diets have been made in adolescents. While weight losses of 9.9 kg have been achieved with a low carbohydrate diet, the levels of LDL-cholesterol have not fallen.(2) On the other hand, with the low fat diet, a weight loss of 4.9 kg and a decrease of LDL-cholesterol levels have been observed. Low carbohydrate diets may be useful for calory restriction. However, the usefulness of these diets is gradually lost over time. The effect on insulin secretion of the fast absorbed, concentrated carbohydrates (i.e., those with high glycemic index) is more

marked than that of protein and fibre taken in high concentrations. The role of glycemic index on weight gain in children is also currently a subject of debate. A relationship between BMI and drinks with artificial sweeteners has been observed in children. It has been shown in adolescents that diets with low glycemic index result in reduced BMI and adiposity. It has been found that with a diet of low glycemic index, consisting of 45-50% carbohydrate and 30-35% fat, the reduction in BMI was 1.3 as compared to 0.7 with a low fat diet. Thus, by excluding carbonated drinks or fruit juices and sports drinks from the diet, obesity will be prevented. Other macrofoods, vitamins and microfoods may modulate the risk of metabolic complications. For example, high fiber intake (with grains and cereals) is associated with lowered risk of T2DM and cardiovascular disease. Soluble and insoluble fibers reduce the absorption of macronutrients, causing increased fat oxidation, and improved glucose tolerance. In children and young adults, magnesium intake (with cereals, hazel nuts and green leaves) and consumption of calcium, vitamin D containing milk products lowers the risk of T2DM.(2) It has been shown that certain foods (e.g., grapefruit, cabbage, potatoe, red pepper, chick pea, fig, carrot, corn, salt and cinnamon) increase, while others (e.g., avocado, raspberry, apple, broccoli, rye bread, macaroni containing bran, brown rice, oats, vegetable soup, almond, linden flower, mozzarella cheese, sardine, fish, frozen yoghurt, egg) reduce the appetite, a point which can be considered for nutritional planning. Salmon, walnuts, seeds and green leafy vegetables rich in omega-3 fatty acids can be recommended. In patients who will undergo planned surgery the use of capsules of omega-3 fatty acids and foods rich in these should be stopped 15 days before the operation because as a result of interactions with other drugs, thrombocytic functions may be adversely influenced.

Exercise: Basal metabolic rate is equivalent to 50-70% of the daily energy consumption. Lean body mass is the main factor determining

the basal metabolic rate. Therefore, exercises aimed at increasing the muscle mass can be recommended. A sedentary lifestyle increases the risk of childhood obesity, preparing the basis for DM and cardiovascular diseases. When regular exercising is combined with restricted calory and fat intake, it has been shown in adults that the progress of DM, glucose intolerance, cardiovascular morbidity and mortality are significantly reduced.(6, 9) With exercise the adipose stores and the visceral fat are reduced to some extent, correspondingly the lean body mass increases and energy spending at rest also increases. Exercise increases the insulin sensitivity of the adipose tissue; decreasing the postprandial levels of free fatty acids (FFA), LDL-cholesterol and TG while raising the level of HDL-cholesterol. The increase in insulin sensitivity and fat oxidation also normalise the functions of the vascular endothelium. The data in hand indicate that obese children benefit from exercising with reduction of metabolic and cardiovascular complications. In a modified cross-controlled study with 79 obese children of 7-11 years of age, a program of 40-minute/day exercise for 5 days, a reduction of 5% in body fat, of 10% in fasting insulin and of 17% in plasma TG levels has been achieved despite a lack of total compliance with the programmed diet.(2) Aerobic exercises have also been found to improve vascular endothelial functions. If exercising is interrupted, the observed improvements show a regression. As BMI increases the voluntary exercising capacity decreases. Therefore, exercising has to be started before the development of morbid obesity and before the individual becomes functionally immobile. The benefits of dieting and exercising in obesity in the short term are very positive. There are difficulties in establishing the ideal lifestyle in the long term. For example, among 1383 obese children in Italy, 30-34% showed noncompliance to dietary regimens in 3 months and 90-94% in 2 years. Obese children should be motivated to walk to school, to walk as an exercise, to take the dog for a walk, to play at intervals and to watch less TV and to spend less time with the

computer. Physical activity is necessary for normal growth and development. Exercising in obese children is important for the strengthening of cardiovascular functions, for increase in muscular power and bone development, fall in blood glucose and lipid levels, for feeling good and gaining self confidence. The daily activity should last at least 60 minutes, although 90 minutes of daily exercise is required for decreasing insulin resistance and the risks of cardiovascular morbidity.(9) Exercising starts glucose and glycogen oxidation immediately but fat oxidation starts after 90-120 minutes. The benefits of exercise last for 24-72 hours. Therefore, in a week, maintained exercising for at least 3 times must be planned.

Sleep: In children with short duration of sleep, the lack of sleep changes the appetite control mechanisms and also time becomes available for snack eating which contribute to the development of obesity. In Turkey, studies in 5358 children of 6-17 years of age in and around Kayseri have shown that in comparison to the children who slept 10 or more hours per day, those who slept 9-10 hours, 8-9 hours and 8 and less hours, the obesity risk was, respectively 1.84, 1.63 and 1.72 fold higher (unpublished data).

Television and computers: Time spent on these activities should not exceed 2 hours in a day.(10)

PHARMACOTHERAPY

If treatment with attempts to modify lifestyle proves to be inadequate, the patient has to be referred to a subspecialist for other possible therapeutic options. In current pharmacotherapy, agents which increase energy expenditure or suppress appetite and gastrointestinal absorption and limit the secretion and the effectiveness of insulin are being used.(2)

Increasing energy spending

Thyroid hormone, dinitrophenol, amphetamines, phenfluramine, phenylpropylamine and ephedrine have been used

with this objective. However, as most of these agents cause significant complications and have even been shown to be life threatening, their use has been largely abandoned. Although caffeine and ephedrine have been tried along with hypocaloric diets in obese children, the undesired side effects make these uncommendable despite achievement of marked weight loss.

Anorectic drugs

The only appetite suppressant agent recommended for use in obese adolescents over the age of 16 is sibutramin which inhibits the neuronal reabsorption of serotonin, norepinephrin and dopamine.(2) This drug may be used along with calory limitation and attempts to change family lifestyle or attitudes. In a study with 43 obese and 39 placebo controls, at the end of 6 months of sibutamine usage, a reduction of 6.8- 8.5% of BMI among the obese versus a reduction of 4.0-5.4% in the controls have been reported. This weight loss has not been observed after the 6th month. Next to the decrease in the fasting insulin levels an increase in the HDL-cholesterol has also been observed. In 19 of the 43 drug treated patients, the finding of mildly raised blood pressure and tachycardia has led to the decrease of the sibutramine dose. This hypertensive effect is due to the vasoconstrictive effect of the drug. Insomnia, headaches and depression may also develop. What needs special attention is the possibility of the development of the serotonin syndrome which is likely with the concurrent usage of MAO inhibitors, buspirone, lithium, mepedrine, selective serotonin reuptake inhibitors (SSRI), tryptophan, dextrometorphan, ergot alkaloids or phentanyl.

Anorectic drugs cannot replace exercise. Weight loss with drugs is achieved in 4-6 months which then, graphically speaking, plateaus off. Upon discontinuation of the drug, weight gain restarts. The usage of drugs for longer than 2 years is not recommended.

Drugs which reduce nutrient adsorption

Orlistat (Xenical) causes the fecal loss of triglycerides by inhibiting the pancreatic lipase. This causes loss of weight in obese adults as well as reducing total and LDL-cholesterol in blood, and also reducing the risk of T2DM and glucose intolerance. Orlistat has been given approval by the FDA to be used in children over 12 years of age. It has been used in obese adolescents together with modification of lifestyle and at the end of a 3-month study period significant reductions in body weight (4.4-4.6 kg), in BMI (1.9-2.5), in total cholesterol (21.3-24.7 mg/dL), LDL-cholesterol (15.8-17.3 mg/dL), fasting insulin (13.7-19.0 mU/L), fasting plasma glucose (7.4-15.4 mg/dL), and an increase in insulin sensitivity have been observed. The response to this drug is variable. Weight reduction of 2.5-12.75 kg, alongside with a reduction in body fat percentage, has been reported in 7 to 12-year old obese and morbid children.

In a study in this country on children with exogenous obesity, weight losses of 5.4 - 6.27 kg were noted in 11 receiving orlistat compared to weight gains of 4.16-6.45 kg in 20 children given exercise and modified diet.(11) In this study 7 patients stopped taking the drug because of the adverse side effects. Reduction in blood levels of vitamins A, D and E have been noted. The reduction of the fat content of the diet during drug treatment is necessary as a measure against flatulence and diarrhea which may lead to the abandonment of the drug by the patient.

Drugs that increase or suppress insulin sensitivity

The synthesis of triglycerides and deposition of fat in the adipose tissue influences insulin secretion. The resultant hyperinsulinemia of eating or the hyperinsulinemia of fasting favours fat deposition and limits fat mobilisation. Drugs which reduce postprandial insulin levels are useful for childhood and adulthood obesity. In this respect the only drug that contributes to the loss of weight is

metformine,(12, 13) which is a short chain derivative of guanidine and activates adenosine monophosphate kinase (AMPK). (14) This enzyme is accepted as a sensor of cellular energy status and is activated by exercise. Metformin primarily acts on the hepatocytes and while increasing hepatic glucose uptake and glycolysis, it decreases gluconeogenesis. It increases glucose uptake, lipid catabolism and insulin sensitivity in muscle tissue.(12) Consequently, food intake is reduced, weight loss begins, fatty acid synthesis declines and fat depots, especially the subcutaneous deposits as compared to the visceral fat, are reduced, the plasma lipid profile is normalised, the progression from glucose intolerance to T2DM is impeded. Also, prevention of certain types of cancers in the obese has been reported.

Two major double blind placebo controlled studies in obese adolescents have been conducted with metformine. In these the family history of T2DM was positive, the patients had insulin resistance without glucose intolerance. In one study the dietary control of the patients was not adequate. In the 29 patients treated with metformine, a decrease of 3.6% in BMI, of 9.8 mg/dL in fasting plasma glucose, of 12 mU/L in fasting insulin, and a reduction in leptin levels were achieved. In the other study with 24 patients, metformine was used alongside a reduced calory diet and decreases in body weight, plasma leptin, glucose, insulin, cholesterol and triglyceride levels were demonstrated.(2)

Atabek and Pirgon(13) have compared the results of 90 obese adolescents given 500 mg metformin twice daily with that of 30 given placebo. In approximately 6 months the drug treated group have shown a fall in BMI, with reduction of nearly 50% in the fasting and the 120-min insulin levels. HOMA-IR scores (as calculated by the homeostasis model assessment of insulin resistance formula) have similarly been reduced by half.(13)

Metformine is generally tolerated well. Transient abdominal problems can be avoided by taking the drug together with meals. Lactic acid accumulation is very rare in pediatric

patients but, it should not be used in the presence of cardiac, hepatic and renal disorders. Also, the risk of development of radiocontrast nephropathy has to be considered.(12) In obese children AST and ALT levels may rise to levels 3 times the normal but metformine can be used in these patients as the hepatic steatosis is improved with metformine administration. In the patients urinary loss of B1 and B6 may increase and B12 absorption may be adversely affected. Therefore, multivitamin backing should be given with metformine. Although the FDA has given approval for metformine usage for treatment of T2DM, this has not been yet granted for usage in pediatric obesity and insulin resistance.

Octreotide: This is an octapeptide that mimics natural somatostatin pharmacologically; it binds somatostatin-5 receptors and reduces insulin secretion. In children with hypothalamic obesity it reduces the insulin secretory response and augments weight loss. However, the cost effectiveness of this agent, given the difficulties of usage, the adverse side effects like disorders of the digestive system, risk of cholelithiasis, suppression of GH and TSH secretion and cardiac dysfunction have limited its generalised prescription. It is indicated for selective and hypothalamic obesity.

Antilipeamic agents: Dyslipidemia is observed in nearly 25% of the pediatric cases of obesity. If the cholesterol levels are in the 170-200 mg/dL range, close observation is required. Cases with levels over 200 mg/dL are put in a program of controlled diet with exercise. LDL-cholesterol levels of 110-119 mg/dL is considered borderline, and 130 mg/dL is regarded as excessive. Children with levels 190 mg/dL and over, or with 160 mg/dL coupled with a family history of cardiovascular risk require treatment(15) which involves the use of statins, the HMG CoA reductase inhibitors in a dose range of 10-40 mg/day.

BARIATRIC SURGERY

Lifestyle changes through diet and exercise or pharmacotherapy may not achieve the

desired results in the long term in some patients. In selected cases and extreme obesity with comorbidity, bariatric or weight loss surgery may be selected.(6) The usually applied methods are laparoscopic gastric banding and Roux-en-Y gastric bypass (RYGB). Gastric banding can cause oesophageal dilatation and achalasia, and gastroesophageal reflux (GER) may increase. There are risks of malposition, malfunction, balloon rupture and infection. Iron deficiency (50%) with RYBG, folate, thiamin, calcium deficiencies (30%), cholecystitis (20%), wound infection and, small gut and gastric blockage (5-10%), atelectasis, pneumonia (12%) and incisional herniation (10%) are other side effects likely to develop.

Further, tracheostomy may be required for preoperative hypercapnia or to keep the airways open post operatively. Fatal pulmonary embolism, gastric dilatation, dumping syndrome are other potential side effects. Mortality rate is 1-5%, and an experienced surgical team is required.

Experience in bariatric surgery in adolescents is limited.

RECENT DEVELOPMENTS

New treatment procedures are being tested on the use of hormonal and active agents which affect hunger and satiety.(17) Cholecystokinin, glucagon-like peptide 1 (GLP-1), and peptide YY3-36 (PYY) are agents which induce satiety. GLP-1 (incretin) is involved in increased satiety, accelerated fat oxidation and energy consumption. The new GLP-1 analogue exenatide and the Dipeptidyl Peptidase-4 antagonist sitagliptin (oral antihyperglycemic agent that prevents GLP-1 destruction) are the new agents used to prevent obesity and DM.

Adiponectin, exclusively secreted from the adipose tissue, plays a role in the suppression of metabolic events that result in obesity, DM and atherosclerosis. It is found to be present in low concentration in the bloodstream of the extremely obese and it may be beneficial in the treatment of obesity.

Amylin secreted by the beta cells of the

pancreatic islets of Langerhans is effective in the reduction of food intake, the delaying of gastric emptying and the decrease in the post-prandial levels of glucagon. Rimonabant, of the cannabinoid-1 receptor blockers, has been associated with reduced appetite, normalisation of fatty liver and insulin resistance as well as significant losses of weight. However, mood changes in the users have been noted.

Topimaratate is a novel anticonvulsant drug that causes loss of appetite resulting in weight loss. Its side effects include depression, memory and concentration disorders.

Carnitine may be useful by accelerating the oxidation of fatty acids. Although some herbal drugs have been proposed as useful agents for obesity, at present definite data for treatment are insufficient.

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