44 *Management of Obesity*

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Abstract: Obesity is increasing in urban areas of India, and constitutes most important factor for development of the metabolic syndrome and diabetes. Long-term management with weight loss is the key component for successful management of the problem. Non-pharmacological management through diet, physical activity, and behavior modifications is the first step and most important step. However, if it fails, pharmacological treatments with drugs are advised. Orlistat, sibutramine, and rimonabant are effective weight loss drugs. However, weight is often regained once these drugs are withdrawn. Orlistat and sibutramine have FDA recommendation, while rimonabant is awaiting approval. Lastly, the patients suffering from morbid obesity and with a very high BMI need surgical intervention. Rational application of these therapies, along with behavioral modification, should lead to significant weight loss and weight loss maintenance.

INTRODUCTION

Obesity is increasing at alarming rates in developed industrialized countries as well as in developing countries undergoing rapid nutrition and lifestyle transition. Reduction in the energy expenditure as a result of mechanization, and an increase in energy intake due to increased availability of low cost, high fat, energy-dense food are largely responsible for its rising prevalence. Obesity is associated with increased risk of chronic diseases like type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), hypertension, dyslipidemia, and certain cancers, and significantly increases the risk of mortality at any given age. Obese persons have a greater mortality risk compared with non-obese persons. Obese subjects have been seen to have a two-fold increased risk of cardiovascular disease-related mortality, and a body mass index (BMI) greater than 35 kg/m^2 has shown a seven-fold increase in the mortality risk in patients with CHD.

Current trend in India indicates that obesity is increasing in children as well as adults**.** The urban prevalence of obesity has increased alarmingly; almost 50% of adult urban Indians in Delhi fulfil criteria for either obesity or abdominal obesity. The prevalence of overweight/obesity in children has increased from 16% in 2002-2004, to 29% in 2006.[1,2] But what is remarkable is that even though BMI values and prevalence of generalized obesity are comparable between Asian Indians living in India and the ones living in US, the abdominal obesity (waist circumference; waist-to-hip-ratio) of Asian Indians living in urban India (specifically New Delhi) has become even greater than Asian Indians living in the US. Rural population, however, living in India still has lower prevalence of obesity and truncal obesity than the urban population (Table 44.1, Unpublished data 2006). The prevalence of obesity-related morbid consequences; primarily the metabolic syndrome and T2DM has also been increasing rapidly**.**

The American Heart Association (AHA) has classified obesity as a major, modifiable risk factor for CHD. The World Health Organization has recently stressed that the economic consequences of obesity are as much as those due to malnutrition. Hence, it becomes imperative

to manage obesity so as to minimize the risk for morbidity and mortality from chronic diseases. Moreover, since childhood obesity is associated with adult obesity, the prevention of obesity in children is key to decreasing the current obesity epidemic.

Various therapeutic approaches are available to manage obesity. Non-pharmacological lifestyle management is the first and, perhaps, the most important step. Pharmacological management becomes necessary if the condition is not treated through lifestyle management, and in the absence of achieving the recommended weight from medications, occasionally, surgical management is exercised.

MANAGEMENT

The key management strategies are summarized in Table 44.2. The mode of management in terms of using pharmacological and surgical methods, apart from non-pharmacological therapies depends on the assessment of risk factors based on the presence of correlated and co-morbid factors (Table 44.3), or based upon the BMI status along with co-morbidities seen in the patients (Table 44.4).

Non-pharmacological Management

There is strong evidence to suggest that the risks of mortality and morbidity associated with obesity can be reduced with weight loss. A 10 kg weight loss was shown to induce a 20-25% decrease in total mortality, and a relatively modest weight loss of 5-10% of pretreatment body weight was seen to be associated with significant improvements in obesity-related co-morbidities such as T2DM, hypertension, and CHD, apart from any decrease in overall mortality.[3] The WHO has recommended initial goal of weight loss treatment is to reduce the body weight by approximately 10% over six months.[4] In Diabetes Prevention Program, aim was to reduce weight in obese persons with impaired glucose tolerance by 7%, which led to the reduction of incidence of new-onset diabetes by 58%.[5]

However, it is difficult for most patients to continue to lose weight after a period of six months, and the emphasis then lies on maintaining the lowered body weight. The principle aims of weight management, thus, are to induce a negative energy balance to reduce body weight immediately and to maintain a lower body weight over the long-term. Several approaches have been described for the non-pharmacological management including diet, physical activity, and behavioral treatment.

Dietary Modifications

The aim of the dietary approach is to achieve a deficit in energy balance of 500-600 kcal/day, resulting in a weight loss of 0.5-1.0 kg/week, and to ensure that these obese patients follow a healthy balanced diet. Dietary interventions, hence, emphasize on energy reduction through low calorie and low fat food choices, increased vegetable and fruit intake, and healthier snacks with decreased portion sizes. Water is recommended as the main beverage, and drinks with high sugar content, including soft drinks and fruit juices should be limited. The effect of these interventions is a reduction in total energy intake by reducing the energy density of the diet (low in saturated fat and high in complex carbohydrate). Long-term changes in food choice, eating behavior, and lifestyle are needed. The two main dietary options are low calorie diets (LCDs) and low fat diets (LFDs).

Low Calorie Diets

More emphasis is put in restricting the total energy intake in LCDs than the macronutrient intake. Various studies have supported the fact that weight loss on calorie-restricted diets is related to energy intake and not the nutrient composition[6]. A meta-analysis has shown that LCDs produced

weight loss regardless of the duration of treatment, and body weight was reduced by an average of 8% over 3 to 12 months compared with controls. Very low calorie diets, providing about 400-500 kcal/day have shown to produce greater initial weight loss, but the long-term (> 1 year) weight loss remains same as that of LCDs.[7]

Low Fat Diets

High fat diet due to its high energy density promotes weight gain and obesity, and more so in sedentary people. Hence, restricting fat intake should be seen as a means of reducing the diet's energy density and total energy intake. A meta-analysis showed that each percentage point reduction in energy from fat led to an achievement of loss of weight up to 1.6 g/day.[8]

Low Carbohydrate Diets

Atkins Diet, a low carbohydrate and a high-fat diet has been popularly used for weight management in past decades, and has shown short-term weight loss probably due to formation of ketone bodies, that cause sodium diuresis and anorexia. Trials have shown weight loss of about 3.3 kg at 6 months with Atkins diet[9]. However, no significant difference in the weight loss at 12 months when compared to low fat diets. Further, subjects on Atkins diet may suffer from constipation due to lack of fiber intake, and renal stones. Lack of long-term compliance is the main drawback with the Atkins diet.

South Beach Diet, a modified form of the Atkins diet, endeavors to replace some of the saturated fat with unsaturated fat, and similar weight loss but better results on lipid levels compared with the Atkins diet are expected. South Beach diet restricts carbohydrates to 40 percent of calories or less, and focuses more on the glycemic index of foods than the Atkins Diet. It advocates the right kind of carbohydrates to minimize dietary glycemic index and recommends a more balanced diet that limits fat and processed or refined carbohydrates. The diet encourages increased fiber intake, which is associated with lowered weight even when total caloric intake is relatively unchanged. Even though trials with South Beach diet are still under evaluation, a moderate carbohydrate, high protein diet has been shown to maintain weight loss at 12 months and beyond, with improvements in cardiovascular risk factors and little risk of long-term side effects.

Unfortunately, trials with low carbohydrate high protein diets in Asian Indian populations are not available. It would be interesting to research the metabolic effects of vegetarian diets modified similar to Atkins and South Beach diets.

Physical Activity

Increased physical activity is important for promoting weight reduction and in maintaining weight loss. Regular physical activity has been shown to reduce medical co-morbidities associated with obesity. Increased physical activity and decreased sedentary behavior, as part of either a planned program or an integrated lifestyle choice, are both important, even though integrated exercising as lifestyle modification has been shown to maintain better weight than the programmed exercising.

Increased physical activity in overweight and obese adults has been evidently shown to reduce the risk of cardiovascular disease, independent of the weight loss.[10] Irrespective of their BMI, moderate to highly fit men have significantly lower age-adjusted risk for all-cause mortality, as compared with sedentary or low-fit men, suggesting the importance of increasing physical activity regardless of weight changes.[11]

Physical activity should be initiated slowly and, depending on progress and capacity, the intensity of exercise could be increased gradually. However, the recommendation of specific guidelines by American College of Sports Medicine promotes an expenditure of 300 to 500 kcal per session and 1,000 to 2,000 kcal per week for adults. Since, this goal may not be realistic for the

severely obese person, it is better to start with moderate levels of physical activity (e.g. brisk walking) for 30 to 45 minutes, and then increase gradually. However, whether more physical activity (~60 minutes daily) is required in Asian Indians needs to be researched. The benefits of resistance exercise have been less researched. We have recently shown improvement in glycemic control, insulin sensitivity and subcutaneous adiposity with daily resistance exercise using small weights (Misra A, unpublished data).

Behavioral Modification

Behavior modification is a component of most weight management programs, and is a systematic method for modifying eating, exercise or other behaviors that may contribute to obesity. Behavior modification techniques include self-monitoring, stress management and social support. The assumptions of behavioral treatment are that patterns of eating and physical activity are learned behaviors and can be modified. Therefore, the goal of behavioral treatment for weight control is to help obese patients identify their eating and activity patterns and thinking habits that contribute to their excess weight. Unless the patient acquires a new set of eating and physical activity habits, long-term weight reduction is unlikely to succeed.

The cornerstone of behavioral treatment is self-monitoring, and has been shown to correlate to successful long-term weight control. For example, patients who tend to snack in the evening, often while watching television, generally do so because of boredom and not hunger, and can be advised to control their snacking by drinking low calorie drinks. The behavioral approach to physical activity is that some activity is better than none. Increase in energy expenditure is desired, without concern for the intensity of activity. In such cases, patients should be advised to use the stairs whenever they can, to stand while on the telephone, park further away from entrances so as to walk more, or other activities integrating them in their daily lifestyle.

Pharmacological Management

Lifestyle modification is helpful for most obese patients, but at times is not sufficient and needs to be supplemented with medications. However, drugs should be used only as part of a comprehensive program that includes dietary modification, physical activity, and behavioral treatment. Guidelines for pharmacotherapy are given in Table 44.3.[12] Even though various drugs have been used, currently the most effective available drugs are orlistat, sibutramine, and rimonabant (Table 44.5).

Orlistat

Orlistat is a potent inhibitor of pancreatic/intestinal lipase and therefore increases fecal fat loss. The effect is dose-related but reaches a plateau with doses above 400-600 mg/day. Thus, reducing fat absorption by binding to lipase in the intestinal lumen, orlistat often leads to steatorrhea, flatus, fecal incontinence and oily spotting. As up to one third of dietary fat is excreted in the stools, patients must adhere to a very low fat diet while taking orlistat, or face unpleasant gastrointestinal side effects. However, since the absorption of fat-soluble vitamins A, D, E, and K may be slightly reduced with orlistat intake due to malabsorption, it would ideally require supplementation of these vitamins. Orlistat has been approved by the FDA for long-term use.

A 12-week treatment with orlistat (360 mg per day) resulted in a weight loss of up to 5 kg compared with 2 to 3 kg losses among patients in the placebo group.[13] Weight losses appear to be dose-dependent, with lower dosages have been seen to produce smaller weight losses. Moreover, sustained weight loss was demonstrated in the orlistat treatment group (120 mg three times daily), with an average weight loss of 3 kg more than the placebo group.[14]

Patients of T2DM treated with orlistat plus a modification of diet showed reductions in dosage of sulfonylurea medications and showed significant improvements in hemoglobin A1c (HbA1c), fasting plasma glucose levels, and lipid parameters when compared with placebo plus diet modifications. Long-term studies lasting two years showed that a quarter to a third of the

weight lost during the first year was regained during the second year of treatment, even though the overall weight loss was still significantly greater than that seen with placebo.[15] However, it is recommended that treatment with orlistat should only be started if diet alone has previously produced a total weight loss of at least 2.5 kg over a period of four consecutive weeks. Treatment should be discontinued after 12 weeks if the patients are unable to lose at least 5% of their initial body weight, and treatment should not usually be continued beyond 12 months.

Sibutramine

Sibutramine inhibits the neuronal reuptake of serotonin, norepinephrine and dopamine. Sibutramine does not stimulate secretion of serotonin, and seems to produce weight loss by its anorectic effect and, possibly, by stimulating thermogenesis (i.e., increasing metabolic rate). Sibutramine has also been approved by the FDA for the long-term treatment of obesity.

Randomized controlled trials have shown that sibutramine produces a dose-related weight loss when given in the range 5-30 mg/day, with an optimal dose of 10-15 mg/day. Studies have shown that active weight loss occurs for the first six months of sibutramine use and can be maintained for up to one year with continued treatment. A one year trial of sibutramine showed that sibutramine dosages of 10 mg per day, 15 mg per day, and placebo resulted in weight loss of 4.8 kg, 6.1 kg, and 1.8 kg, respectively, and led to significant reductions in waist-to-hip ratio compared to patients receiving placebo.[16] Another study demonstrated significant, dose-dependent weight loss over 24 weeks with sibutramine; however, like other studies, it showed that weight gain occurs with discontinuation of the drug.[17] A long-term two year study found that even though there was a tendency of weight gain in both the sibutramine and placebo groups during the second year of follow-up, weight losses were significantly greater among those who received sibutramine for the full two years of the study.[18] The potential long-term treatment benefits of sibutramine in weight management is currently being assessed in the landmark **S**ibutramine **C**ardiovascular **OUT**comes study **(SCOUT),** which is the first prospective study to examine the role of obesity management in relation to cardiovascular disease.

Treatment with sibutramine has been also shown to improve many obesity-related co-morbidities.[19] In a 12-week study, patients with T2DM who received sibutramine showed moderate but significant weight loss as well as improvements in HbA1c levels, compared with patients in the placebo group. Sibutramine-induced weight loss produces favorable reductions in plasma triglycerides, total cholesterol, low-density lipoprotein cholesterol and HbA1c levels.[16]

The starting dose of sibutramine should normally be 10 mg/day. The continuation of treatment beyond three months should be supported by evidence of a loss of at least 5% of the initial body weight. Treatment with sibutramine is not usually recommended beyond 12 months. The most common side effects seen during treatment with sibutramine are headache, dry mouth, constipation, and insomnia. Sibutramine has a tendency to raise blood pressure, and this effect is dose-related, thus limiting its use in hypertensive patients. It causes an increase of 1 to 3 mm Hg in systolic and diastolic blood pressure with an increase in the pulse rate. Hence, treatment with sibutramine is not recommended for patients whose blood pressure before the start of treatment is above 145/90 mm Hg. Sibutramine should not be used to treat patients with a history of CHD, congestive cardiac failure, cardiac arrhythmias, stroke, major eating disorders, or psychiatric disorders. Sibutramine should not be used with drugs such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors. In addition, because sibutramine is metabolized by cyto-chrome P450, it may interfere with the metabolism of many other common drugs.

Rimonabant

Rimonabant is an antagonist agonist at the endocannabinoid receptor type 1 (CB1). Rimonabant probably acts by modulating central and peripheral synaptic neurotransmission seen in the endocannabinoid systems, which are one of the brain pathways concerned with central

regulation of body weight and adipose tissue function. CB1 receptor is acted upon by cannabis and related compounds to increase appetite. Experimental studies have shown that the system is over-activated in obesity, and rimonabant antagonizes it. Rimonabant can also exert its own intrinsic actions, and these may be viewed as evidence of either the inverse agonist nature of rimonabant or of tonic activity of the endocannabinoid system.[20] This drug would be available in India early 2007.

Trials have shown that, when combined with a low-calorie diet, rimonabant 20 mg/day leads to an average weight loss of 4 or 5 kg more than placebo after one year of treatment, and the weight loss is similar to as reported with orlistat (indirect comparison). Effects on the lipid profile are similar to those reported with sibutramine. However, patients on rimonabant were shown to regain the weight they lost within about 9 months after rimonabant withdrawal.[21] RIO trial, a large phase 3 program [RIO-Europe and RIO-North America (NA)], evaluated the efficacy and safety of rimonabant (5 or 20 mg/day) in obese or overweight patients. Trials with or without co-morbidities, like untreated dyslipidemia (RIO-Lipids) or with T2DM treated with metformin or sulfonylurea (RIO-Diabetes) were undertaken. It was seen that at dose of 20 mg/day, rimonabant consistently increased weight loss, reduced waist circumference, increased high-density lipoprotein cholesterol (HDL-C) levels, lowered triglyceride levels, diminished insulin resistance, and reduced the metabolic syndrome.[22] Similar improvements were seen in the RIO-Lipids trial at 1 year, and these results were consistently maintained over 2 year in RIO-NA. The RIO-Europe and RIO-NA trials showed that improvements in HDL-C and triglyceride levels with rimonabant over 1 y, compared with bodyweight, were attributable to beyond weight loss alone (40 and 55% for HDL-C and triglycerides, respectively in RIO-Europe and 58 and 47%, respectively in RIO-NA). Additionally, in RIO-NA, changes in fasting insulin and homeostasis model assessment insulin resistance (HOMA-IR), also seemed to improve beyond that seen with weight loss alone, being 50 and 51%, respectively.[23] Since almost half of the metabolic effects, including increase in levels of adiponectin seems to occur beyond that seen with weight loss alone, it suggests a direct peripheral effect of rimonabant. The presence of CB1 receptors in adipose tissue and the recently reported effect of rimonabant on adiponectin production by adipose cells probably represent the key factors responsible for the weight loss-independent effects on metabolic parameters.[21]

Overall, studies show that rimonabant could be useful for the management of clustering cardiovascular disease risk factors or the metabolic syndrome in high-risk abdominally obese patients through its effects not only on energy balance but also on adipose tissue metabolism.[21]

Rimonabant is well tolerated, and the majority of adverse events reported have been mild and transient, and occurred early in the treatment period. Adverse effects of rimonabant include mental disorders (anxiety, depression), neurological disorders (dizziness) and gastrointestinal disorders (nausea, diarrhea). Since, no post marketing safety data are available, the possible long-term adverse effects of rimonabant are unknown and poorly documented.[21] Some experts feel that in view of the lack of adequate data on safety and tolerability profile, it may not be wise to use rimonabant in management of obesity.

Bariatric Surgery

Surgery is the last possible option and it is recommended after thorough assessment and under mandatory postoperative care and monitoring. The occasional use of surgical interventions becomes necessary when other treatments fail. This is discussed in detail in next chapter.

Prevention of Obesity

Prevention of obesity through educative counseling, awareness, and consistent application of lifestyle therapies is possible and also leads to prevention of morbidities. Targeting younger generation to inculcate healthy lifestyle habits through community programs, both nationally as well as internationally, to combat obesity has shown promising results. School-based programs

conducted internationally have showed beneficial trends in the children exposed to the intervention by resulting in lowering of their levels of body fat. Hence, school-based programs focusing on adapting healthy lifestyle factors like spending less time in sedentary activities like television viewing, decreasing consumption of high calorie fatty fast foods, increasing fiber intake though fruit and vegetables, and increasing moderate and vigorous physical activity are needed.

A couple of such programs, namely "*CHETNA"* (*Hindi* for "The Awareness") [Children *H*ealth *E*ducation *T*hrough *N*utrition and Health *A*wareness program], and "MARG" (*Hindi* for "The Path") [*M*edical Education for Children/*A*dolescents for *R*ealistic Prevention of Obesity and Diabetes and for Healthy A*g*eing] are currently being run by our group under aegis of Diabetes foundation (India). The objectives of these programs are to make children aware about obesity and diabetes and educate them regarding the beneficial effects of healthy diet and increase in physical activity. While CHETNA focuses primarily on health education and awareness of healthy lifestyle in schoolchildren, MARG is directed towards both educative awareness and its impact and consequences in helping reduce obesity. Both the programs hope to improve several aspects of obesity-related knowledge, attitudes, and behaviors in these school children with an aim to produce significant changes in preventing obesity by decreased fat intake and increased physical activity.

SUMMARY

Obesity is a chronic disease with no known cure. A decline in energy expenditure not matched by an equivalent reduction in energy intake has led to increased prevalence of obesity, and this is now happening in India due to rapid nutritional transition and urbanization. Long-term management with weight loss is the key component for successful management of the problem. Non-pharmacological management through diet, physical activity, and behavior modification is the first step. However, if it fails, pharmacological treatments with drugs are advised. Orlistat, sibutramine, and rimonabant are effective drugs. Orlistat and sibutramine have FDA recommendation, while rimonabant is awaiting approval. Lastly, the patients suffering from morbid obesity and with a very high BMI need surgical intervention.

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