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Management of Obesity: Results of SCOUT Trial

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Introduction

Obesity is increasing at an alarming rate in developed industrialized countries as well as in developing countries which are undergoing rapid nutrition and lifestyle transition. Substantial changes in lifestyle (greater consumption of energy dense foods, inactive lifestyle etc.) are the predominant reasons for increase in prevalence of obesity and related disorders.[1] Obesity is associated with increase in risk of diseases like type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), hypertension, dyslipidemia, the metabolic syndrome and certain cancers significantly increases the risk of mortality at any given age. Obese subjects have a two-fold increased risk of cardiovascular disease-related mortality, and a body mass index (BMI) greater than 35 / m^2 has shown a seven-fold increase in the mortality risk in patients with CHD.

Table 1 : Comparative Statistics of Obesity between Asian Indians in US and India

Variables	Asian Indians (US)*	Asian Indians (Urban)**	Asian Indians (Rural)***
Mean BMI	25.4	24.8	21.9
BMI > 30	11%	13%	2%
BMI > 23	73.3%	65.4%	31.8%
High WC (cm)	22.5%	38.6%	7.7%
Mean WHR	0.89	0.94	0.84
WHR > 0.90	43.8%	65.7%	23%

All BMI values in kg/m^2; WC, Waist circumference; WHR, Waist-to-hip-circumference ratio

6 cities in USA, **, New Delhi; ***, Gandhigram, South India

Ref: Misra R, Misra A, et al. AAPI-CDC Project, 2004-2006 (Unpublished data)

Secular trends of obesity in India indicate an increasing prevalence of obesity, diabetes and related cardiovascular risk factors not only in adults but also in the younger population.[1,2] The urban prevalence of obesity has increased alarmingly; almost 50% of adult urban Indians in Delhi fulfill criteria for either obesity or abdominal obesity (Table 1, Misra A, unpublished data 2006). The prevalence of overweight/obesity in children has increased from 16% in 2002-2004, to 29% in 2006.[3] Interestingly as compared to migrant Indians, native Indians have similar prevalence of generalized obesity (BMI) but greater abdominal obesity as estimated by waist circumference and waist-to-hip-ratio. The rural populations in India still has lower prevalence of both generalized obesity and truncal obesity when compared to the urban population (Table 1, Misra A, unpublished data 2006).

Clustering of risk factors known as the metabolic syndrome is often associated with obesity and abdominal adiposity, and it is particularly prevalent

Table 2 : Management of Obesity: Key Strategies

Behavioral strategies	Using strategies like self-monitoring, social support, and stress management, etc.
Dietary intake	Reducing caloric intake by 500 to 1,000 kcal per day to produce weight loss.
Physical activity	Obese patients to start with moderate levels of physical activity (e.g., brisk walking or jogging) for 30 to 45 minutes, three to five days per week, and then on all days of week.
Adjunctive pharmacotherapy	Drug treatment to be considered for patients with a BMI ≥ 30*, or with a BMI ≥ 27* in combination with other medical co-morbidities.
Surgery	Surgery to be considered as the last choice when all other modalities fail, and patients with BMI ≥ 40 or between 35 and 40 along with co-morbidities require surgical intervention.*

All BMI values in kg/m^2

* The BMI limits have been assigned in general to all ethnic groups; however, these are lower in Asian populations.

in Asian Indians and south Asians.[4] Insulin resistance and the metabolic syndrome are also becoming more prevalent in children in urban India.[5] We are also witnessing obesity-related morbidities in children and adolescents (polycystic ovarian syndrome, dyslipidemia etc.) If appropriate prevention and treatment approaches are not implemented, we shall witness further increase in twin epidemics of diabetes and cardiovascular disease.

The aim of this brief review is to give overview of the management of obesity and focus on recent data on sibutramine.

Management

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 satisfactorily treated through lifestyle management. Finally, if weight loss is not achieved by pharmacotherapy, occasionally, surgical management is exercised in morbidly obese patients.

Table 3 : Management Recommendations According to BMI

BMI ≤ 27 with or without co-morbidities*	Lifestyle management with diet, physical activity and behavioral modifications. Pharmacological management not used.
BMI > 27 and ≤ 30, without co-morbidities*	Lifestyle management with diet, physical activity and behavioral modifications. Pharmacological management not advised, but can be considered if patient does not respond, or is non-compliant with lifestyle management.
BMI > 27 and ≤ 30, with co-morbidities*	Pharmacological management recommended along with lifestyle changes
BMI > 30 and ≤ 35 with or without co-morbidities*	Pharmacological management recommended along with lifestyle changes
BMI > 35 and ≤ 40 without co-morbidities*	Pharmacological management recommended along with lifestyle changes
BMI > 35 and ≤ 40 with co-morbidities*	Consider surgical management along with pharmacological and non-pharmacological management.
BMI > 40	Consider surgical management along with pharmacological and non-pharmacological management.

All BMI values in Kg/m^2.

* The BMI limits have been assigned in general to all ethnic groups; however, these are likely to be lower in Asian populations.

The key management strategies including diet, exercise, behavior modifications, drug treatment and surgical treatment are summarized in Table 2. The details of these management strategies have been discussed in our previous publications. Briefly, the therapy in terms of using a particular modality depends on the assessment for detecting presence of various cardiovascular and other co-morbid factors (Tables 3 and 4). These guidelines give a general idea about when to apply a particular treatment modality.

In India, currently three drugs (orlistat, sibutramine and rimonabant) have been licensed as anti-obesity drugs.

Table 4 : Pharmacological Management of Obesity

Medication	Mechanism of action	Side effects	Dosage
Sibutramine	Reuptake inhibitor of serotonin, norepinephrine and dopamine. Blocks NE and 5-HT uptake	Elevated blood pressure, tachycardia, headache, insomnia, constipation, dry mouth	10 mg daily initially; can increase to 15 mg daily after 4 weeks in non-responders
Orlistat	Reversible lipase inhibitor. Blocks gastric and pancreatic lipases and causes fat malabsorption	Fecal incontinence, oily spotting, flatulence, vitamin malabsorption	120 mg three times daily just before meals
Rimonabant	Endocannabinoid CB1 receptor antagonist. Causes decreased appetite and has effects of adipocytes	Mild and transient, Nausea, dizziness, Anxiety, depression	20 mg per day

5 HT - 5 hydroxytryptamine; NE - Norepinephrine

Sibutramine

Sibutramine has been used as a weight loss therapy successfully. It 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). It has also been approved by the Food and Drug Administration, USA 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.[6] Another study demonstrated significant, dose-dependent weight loss over 24 weeks with sibutramine; however, like other studies, it showed that weight gain occurs after discontinuation of the drug.[7] 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.[8] Treatment with sibutramine has been also shown to improve many obesity-related co-morbidities.[9] In a 12-week study, patients with T2DM who received sibutramine showed moderate but significant weight loss as well as improvements in HbA_{1c} levels, compared with patients in the placebo group. Sibutramine-induced weight loss produces favorable reduction in plasma triglycerides, total cholesterol, low-density lipoprotein cholesterol and HbA_{1c} levels.[6]

The potential long-term treatment benefits of sibutramine in weight management is currently being assessed in the landmark Sibutramine Cardiovascular Outcome study (SCOUT), which is the first prospective study to examine the role of obesity management in relation to cardiovascular disease.

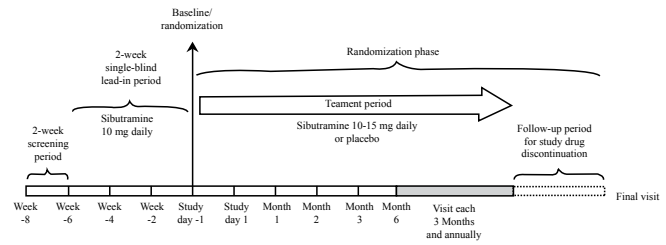
Sibutramine Cardiovascular Outcome Trial

The question of whether the use of Sibutramine can prevent cardiovascular morbidity and mortality has not been studied so far. The SCOUT was designed to determine whether weight reduction with sibutramine would be associated with reduction of cardiovascular endpoints in high-risk overweight and obese patients.

Study Design

Study Population

Age: 55 years or older. BMI: ≥ 27 kg/m^2 and < 45 kg/m^2 or ≥ 25 kg/m^2 and < 27 kg/m^2 with waist circumference ≥ 102 cm (males) or ≥ 88 cm (females)



Classification of risk group categories:

1. T2DM only (24%): subjects with T2DM and another risk factor, excluding cardiovascular disease
2. Cardiovascular disease only (16%): subjects with cardiovascular disease, excluding T2DM and another risk factor
3. Cardiovascular disease + T2DM (60%): subjects with cardiovascular disease and T2DM and another risk factor

The initial data for the lead in period of 6 weeks, which has been recently published.[10] The following is the summary of the data.

- Despite being lighter, with lower predicted lean body mass and higher proportion with diabetes, women lost at least as much weight as men.
- Changes during the 6-week period for body weight, BMI and waist circumference were statistically significant ($P < 0.001$).
- Overall, 6-week treatment period with Sibutramine, with 10 mg dose and weight management resulted in clinically important reduction in body weight and waist circumference in women.
- Treatment with Sibutramine for 6 weeks in normotensive high-risk patients resulted in small median increases in BP consistent with changes seen in the labeled population.
- In patients classified as hypertensive, Sibutramine reduced BP even in those patients already receiving ≥ 2 classes of medications for BP control.

SCOUT trial: Conclusion

Weight management with sibutramine 10 mg is well tolerated by a broad range of high-risk subjects with cardiovascular disease.

1. Clinically relevant and statistically significant median decrease in weight (2.2 kg) and waist circumference (2 cm)
2. Small significant decrease in median systolic and diastolic blood pressure (-3.0 & -1.0 mmHg) and a small significant increase in median pulse rate (+1.5 bpm)
3. Number of serious adverse events (SAEs) and discontinuations for adverse events (AEs) was lower than might be anticipated for these high-risk patients and in general, were similar to those reported previously with sibutramine therapy and reflect its mode of action.

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