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# Management of the Metabolic Syndrome and the Obese Patient with Metabolic Disturbances: South Asian Perspective

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## Abstract

There is an increased prevalence of obesity and the metabolic syndrome (MS) among South Asians. The phenotypes of obesity and body fat distribution are different in South Asians; they have high body fat, intra-abdominal and subcutaneous fat and fatty liver at a lower body mass index compared to white Caucasians; this has led to the frequent occurrence of morbidities related to a higher magnitude of adiposity [e.g. type 2 diabetes mellitus (T2DM), hypertension (HTN) and dyslipidemia]. The increasing prevalence of obesity and related diseases in the South Asian population requires aggressive lifestyle management including diet, physical activity and, sometimes, drugs. For therapeutic interventions, several drugs can be used either as mono- or combination therapy. Drugs like orlistat, which is used for the management of obesity, also reduce the risk of T2DM. Similarly, HMG CoA reductase inhibitors decrease low-density-lipoprotein cholesterol levels and reduce the risk of cardiovascular diseases. However, some drugs used for the treatment of HTN (e.g.  $\beta$ -blockers) may increase the risk of hyperglycemia and therefore need to be used with caution. Finally, to prevent obesity, MS and T2DM among South Asians, it is particularly important to effectively implement and strengthen population-based primary prevention strategies.

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## Introduction

A rapid increase in obesity and related noncommunicable diseases, including type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia and cardiovascular diseases (CVD), is occurring in South Asian countries. Insulin

resistance and clustering of proatherogenic, cardiovascular risk factors, also known as the metabolic syndrome (MS), are frequently seen in South Asians, even at a young age [1].

Increasing urbanization, rapid nutrition transition and the consequences of imbalanced nutrition combined with a sedentary lifestyle are the factors contributing to obesity. Persistent obesity dysregulates the metabolic processes, including the action of insulin on glucose, lipids and free fatty acid metabolism, causing hyperglycemia, dyslipidemia, HTN and MS. Obesity and MS are immediate precursors of T2DM and CVD [2].

The purpose of this article is to briefly review obesity and MS focusing on South Asians and then discuss the management of these patients. Literature search was carried out using the terms obesity, insulin resistance, metabolic syndrome, diabetes, dyslipidemia, hypertension, nutrition, physical activity, pharmacotherapy, Asian Indians and South Asians in PubMed from 1980 to March 2014.

## **Definitions**

### *Obesity*

Obesity is defined as an excessive accumulation of fat in the body resulting in adverse effects on health of the individual (table 1) [3]. The most widely used method to define thinness and fatness is body mass index (BMI; a ratio of weight in kilograms divided by height in meters squared). Abdominal obesity is defined by waist circumference (WC). As per the consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians, both BMI and WC should be used together (using Asian Indian-specific cutoffs; table 1) with equal importance for population- and clinic-based metabolic and cardiovascular risk stratification [4]. The cutoffs as defined for Asian Indians are lower than the international criteria in view of the high body fat and occurrence of morbidities with lower BMI values compared with white Caucasians [1].

### *The Metabolic Syndrome*

MS is defined as a clustering of cardiovascular risk factors in an individual which predisposes the person to a greater risk of developing T2DM and CVD. According to the consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians, three out of five factors have to be abnormal for the identification of MS. It includes previously diagnosed patients with HTN, high triglycerides (TG), low high-density-lipoprotein cholesterol (HDL-c), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or T2DM, and those on

**Table 1.** Defining obesity, abdominal obesity, MS, dyslipidemia, HTN and hyperglycemia in Asian Indians

Generalized obesity <sup>a</sup>	Abdominal obesity <sup>a</sup>	MS <sup>a</sup>	Dyslipidemia <sup>a</sup>	HTN <sup>b</sup>	Hyperglycemia [7]
<i>BMI cutoffs</i>	<i>WC cutoffs</i>	<i>WC</i>	<i>Total cholesterol</i>	<i>Pre-HTN</i>	<i>IFG and FPG concentrations</i>
Normal	Men	Men >90 cm	≥200 mg/dl	SBP 120–139 mm Hg	≥100 and <126 mg/dl
18.0–22.9	>90 cm	Women >80 cm	<i>TG</i>	DBP 80–89 mm Hg	<i>IGT</i>
Overweight	Women	(nonobligatory)	≥150 mg/dl	<i>HTN</i>	Elevated 2-hour FPG
23.0–24.9	>80 cm	<i>Blood glucose</i>	<i>LDL-c</i>	SBP ≥140 mm Hg	≥140 and <200 mg/dl after
Obesity		≥100 mg/dl	>100 mg/dl	DBP ≥90 mm Hg	a 75-gram OGTT in the
>25		<i>HTN</i>	<i>HDL-c</i>	<i>Consensus guidelines<sup>a</sup></i>	presence of an FPG
		≥130/≥85 mm Hg	Males	SBP ≥130 mm Hg	concentration <126 mg/dl
		<i>TG</i>	<40 mg/dl	DBP ≥85 mm Hg	<i>Diabetes</i>
		≥150 mg/dl	Females		FPG ≥126 mg/dl
		<i>HDL-c</i>	<50 mg/dl		
		Males <40 mg/dl			
		Females <50 mg/dl			

SBP = Systolic BP; DBP = diastolic BP; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test.

<sup>a</sup> As used in the consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians [4, 6].

<sup>b</sup> Classification according to JNC VII (Seventh Report of the Joint National Committee) criteria [6].

treatment for the above disorders. This definition is similar to the modified National Cholesterol Education Program, Adult Treatment Panel III definition with ethnic-specific definition of WC (table 1) [4].

### *Dyslipidemia*

Dyslipidemia signifies the increased concentration of total cholesterol and low-density-lipoprotein cholesterol (LDL-c), decreased concentration of HDL-c and hypertriglyceridemia present alone or in combination. A combination of lipid abnormalities, elevated serum TG, small LDL-c particles and low HDL-c are metabolically interlinked and have been termed as ‘atherogenic dyslipidemia’ [5].

### *Hypertension*

The classification of pre-HTN and HTN as per the criteria of the Seventh Report of the Joint National Committee has been provided in table 1, along with the cutoffs by consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians [4, 6].

### *Hyperglycemia*

Hyperglycemia covers both IFG, IGT as well as diabetes mellitus. IFG and IGT represent intermediate states of abnormal glucose regulation, termed prediabetes. The cutoffs for the diagnosis of these diseases have been explained in table 1 [7].

## Management

Therapeutic intervention may benefit persons having obesity, MS, dyslipidemia or T2DM who have an increased risk of developing CVD, with advice on exercise and diet being an essential part of all treatment plans.

### *Dietary Management*

Rapid nutritional transition has resulted in excess consumption of calories, saturated and trans-fatty acids, simple sugars and salt, and low fiber intake in developing countries in South Asia. In combination with a sedentary lifestyle, this has led to an increase in obesity and related disorders. In the following, general guidelines are described, but they need to be tailored to the individual patient.

### *Energy*

The energy requirements suggested are based on the activity profile (sedentary, moderate or heavy), age, gender and physiological status of an individual. Ideally, BMI should be maintained between 18 and 22.9 among Asian Indians [2].

### *Carbohydrates and Fibers*

Carbohydrates form an important component of the diet and are divided into simple and complex carbohydrates. Complex carbohydrates, as consumed by Asian Indians (e.g. whole wheat, brown rice, millets and legumes), should be preferred over refined carbohydrates. Preference should be given to foods with a low glycemic index (e.g. oats, unpolished rice, whole pulses, beans and legumes), while foods with a high glycemic index (e.g. refined flour and root vegetables: yam, potato and tapioca) should be avoided. Simple sugars like crystalline sugar, sugarcane juice, sweetened carbonated beverages, fruit juices and sugar syrups should also be avoided [2].

### *Fibers*

A diet high in natural fibers helps in regulating blood glucose and lowering of cholesterol levels. The total dietary fiber in the daily diet should be at least 25–40 g/day. A minimum of 5–6 servings/day of fruits and vegetables is recommended [2]. Whole grains, cereals, pulses, vegetables and fruits contain high dietary fiber and should be incorporated in the diet.

### *Proteins*

Protein intake should be based on body weight. In conjunction with energy intake, the protein intake should provide 10–15% of the total calories/day in sedentary to moderately active individuals [2]. However, in cases with renal

complications, its consumption needs to be closely monitored under strict medical supervision and modified accordingly. Red meats should be replaced with leaner cuts of meats (chicken/fish). South Asians are predominantly vegetarians, thus high-quality protein is not available to the body; it is therefore required to include low-fat dairy products (milk, buttermilk, cottage cheese or curd) along with other vegetarian sources (soy, pulses or whole grams).

### *Fats*

Fats should not provide more than 30% of total energy/day and saturated fatty acids should provide no more than 10% of the total energy/day. For individuals having LDL-c levels  $\geq 100$  mg/dl, saturated fatty acids (butter, clarified butter or full-fat dairy products) should be  $<7\%$  of the total energy/day. Essential polyunsaturated fatty acids (PUFA) such as linoleic acid should provide 5–8% of the total energy/day and  $\alpha$ -linolenic acid should be 1–2% of the total energy/day. *Cis*-monounsaturated fatty acids (olive, mustard, rapeseed, rice bran and groundnut oil) should provide 10–15% of the total energy/day. Trifluoroacetic acids (partially hydrogenated vegetable oils: vanaspati, margarine and reheated oils) are best avoided or should be  $<1\%$  of the total energy/day. Cholesterol intake should be limited to 200–300 mg/day [2]. Complete dependence on just one vegetable oil does not ensure optimal intake of various fatty acids, therefore use of two or more vegetable oils is recommended.

### *Salt*

Dietary sodium content is an important determinant of blood pressure (BP). Regulating salt intake becomes important in case of MS or if obesity is accompanied with HTN [6]. It is recommended that the total salt intake should be  $<5$  g of sodium chloride (or about 2 g of sodium) per day [2]. Dietary intake of sodium from all sources (pickles, chutneys, processed foods/snacks, bakery items, sauces, preserved meat products, other pre-prepared and preserved foods, soups or cheese) should be limited.

### *Weight Loss Diets*

The quantity and quality of a diet along with physical activity forms an integral component of approaches dealing with weight loss. Studies have shown the possibility to modulate body weight and composition by changing dietary composition. Numerous studies have been done in the developed countries for weight loss in individuals with obesity using different diets targeted at weight reduction, e.g. the Pritikin Principle, Nutrisystem advanced, Ornish Diet or Weight Watchers Diet; however, the efficacy of these or similar diets is yet to be researched in South Asians [8].

**Table 2.** Summary of consensus physical activity guidelines for Asian Indians [9]

Disorders	Physical activity <sup>a</sup> guidelines
Obesity	Moderate-intensity aerobic exercise: 60 min/day Vigorous-intensity exercise 60 min 3 or more days/week
Coronary heart disease (CHD) and HTN	The exercise sessions should be individualized according to the cardiac and physical status of the patient Usually, 210 min/week of moderate-intensity physical activity should be achieved Depending on the clinical condition, a low-intensity, individualized, supervised exercise program could also be devised
Diabetes	Daily physical activity of 60 min in duration including 10–15 min of resistance exercise and work-related activity

<sup>a</sup> Definitions of physical activity intensity levels are provided in the box below.

### Box

#### *Definitions of Physical Activity Intensity Levels [9]*

- (1) Low-intensity physical activity elicits a slight increase in breathing rate and is relative to a given individual (e.g. strolling <3 km/h on level firm ground, tidying the house, leisurely stationary cycling <50 W or <16 km/h and cooking)
- (2) Moderate-intensity physical activity elicits a moderate, noticeable increase in depth and rate of breathing while still allowing comfortable talking and is relative to a given individual (e.g. purposeful walking 3–6 km/h on level firm ground, water aerobics, cycling outdoors for pleasure at 19–23 km/h, cleaning the house, hiking and gardening)
- (3) Vigorous-intensity physical activity elicits a noticeable increase in depth and rate of breathing and will not allow an individual to speak more than a few words without pausing for breath (e.g. walking 1 km in less than 10 min, jogging, cycling outdoors at 23–26 km/h, aerobic dancing and jumping rope)

### *Physical Activity*

It is believed that a sedentary lifestyle is an important factor contributing to the development of T2DM and coronary heart disease (CHD) in Asian Indians. Regular physical activity reduces the risk of obesity, dyslipidemia, HTN and T2DM, and has shown to reduce the risk of CHD. Positive outcomes of moderate-intensity physical activity include an increase in HDL-c levels, reduction in BP, long-term maintenance of weight loss and a decreased risk of death from lifestyle-related diseases [9]. The consensus physical activity guidelines for Asian Indians have been summarized in table 2.

**Table 3.** Treatment for obesity according to BMI category [adapted from ref. 10]

Treatment	25–26.9 <sup>a</sup> 23+ <sup>b</sup>	27–29.9 <sup>a</sup> 25+ <sup>b</sup>	30–34.9 <sup>a</sup> 27+ <sup>b</sup>	35–39.9 <sup>a</sup> 32.5+ <sup>b</sup>	>40 <sup>a</sup> 37.5+ <sup>b</sup>
Diet, exercise, behavior	+	+	+	+	+
Pharmacotherapy		with comorbidities	+	+	+
Bariatric surgery				with comorbidities	+

+ = Applicable. <sup>a</sup> International guidelines. <sup>b</sup> Consensus guidelines for Indians [4].

### Cautions Regarding Physical Activity

(1) For all patients, all decisions regarding the initiation of exercise programs should be taken in consultation with a physician/diabetologist after undergoing a pre-activity evaluation.

(2) Sudden commencement or acceleration of physical activity or any high-intensity exercises should be avoided.

### Therapeutic Management

Individuals with obesity, MS, dyslipidemia, HTN or T2DM have an increased risk of developing CVD and can therefore benefit from therapeutic interventions. Since these conditions typically coexist in an individual, a multidrug therapy may be needed.

#### *Obesity*

Treatment of obesity needs to be quite specific according to BMI category (table 3). There are few drugs available for weight loss although research is ongoing and there may be more options in the future. It is important to note that the weight loss associated with medication use is not continuous and drug withdrawal may be associated with weight gain.

#### Orlistat

Orlistat acts by inhibiting pancreatic lipase resulting in the partial blocking of intestinal digestion and absorption of dietary fat. It can result in a modest weight loss, but major limitations are the associated gastrointestinal

symptoms [11]. It is the only drug approved for long-term treatment of obesity in India and the only drug approved for treatment of obesity in children. In addition, it may lower BP and decreases the risk of T2DM development. Gastrointestinal side effects include cramps, fecal urgency and oily spotting/evacuation.

### Metformin

Metformin has been shown to cause weight loss [12]. DPPOS (Diabetes Prevention Program Outcomes Study) showed that the weight loss caused by metformin was maintained in the 10-year follow-up study of patients with IGT and these patients also had a lower incidence of diabetes compared to the placebo group [13].

### Glucagon-Like Peptide Analogues

Long-acting glucagon-like peptides (GLP-1) receptor agonist, e.g. liraglutide and exenatide, are used for the treatment of diabetes and can cause significant weight loss, approximately 6–8 kg/6 months. These drugs are associated with satiety and decreased gastric emptying [14, 15]. Currently, they are off-label drugs for the treatment of obesity in nondiabetic subjects.

### Phentermine

It is an appetite suppressant and has been approved by US Food and Drug Administration for short-term use (up to 12 weeks); however, it has shown to have psychological dependence. Further, rebound weight gain can also occur once drug tolerance develops [16].

A phentermine-topiramate combination pill is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults in the presence of at least one weight-related comorbidity, such as HTN, T2DM or dyslipidemia. The combination of phentermine and topiramate (extended release) results in a mean weight loss of 8–10 kg [11].

### Lorcaserin

It is a serotonin-2C agonist also known as an appetite suppressant. It is prescribed for weight loss and can produce a mean weight loss of 4–7 kg [11].

### Other Drugs

The following drugs can also be considered as options for the treatment of obesity:

- Diethylpropion (selective norepinephrine-releasing agent)

- Phenylpropanolamine (norepinephrine-releasing agent)
- Bupropion and fluoxetine
- Tesofenasine

### Surgical Options

Patients with severe obesity with or at risk of comorbidities should be offered surgical treatment. Surgical options include the following:

*Liposuction.* It is the removal of subcutaneous fat through large-volume liposuction.

*Bariatric Surgery.* Bariatric surgery is an appropriate treatment for people with T2DM and obesity not achieving recommended treatment targets with medical therapies, especially when there are other major comorbidities. It can be considered for Asian Indians with a BMI above 32.5 with comorbidity and BMI above 37.5 without comorbidity. Many of the MS manifestations have shown potential reversal after bariatric surgery [17].

*Intragastric Balloon.* This inflated saline-containing balloon, which is inserted into the stomach, increases the sensation of fullness. However, there is little additional benefit regarding weight loss and its cost should be considered against a program of eating and behavioral modification.

### *Dyslipidemia and the Metabolic Syndrome*

#### Statins

Statins reduce plasma LDL-c levels and have moderate effects on TG and HDL-c levels. Statins are also thought to raise HDL-c levels by reducing the rate of cholesteryl ester transfer protein-mediated flow of cholesterol from HDL-c. They are highly effective at preventing morbidity and mortality from CVD and can slow the development of atherosclerosis [18]. However, in a meta-analysis of over 90,000 individuals, it was found that statins were associated with a 9% increased risk of developing T2DM (odds ratio 1.09; 95% confidence interval 1.02–1.17), but the benefits of statin therapy clearly outweigh this risk in those with higher baseline risk of CVD [19].

#### Fenofibrate

These fibric acid derivatives (fibrates) are selective agonists of the peroxisome proliferator receptor- $\alpha$ . They reduce TG levels significantly [20]. Although they are generally well tolerated, there have been concerns about the risk of muscle disorders in patients cotreated with statins and fibrates. Studies indicate that monotherapy with statins or fibrates is associated with a low risk of myopathy and rhabdomyolysis, but this risk increases significantly in combination treatment of statins and fibrates; hence ESC/EAS

(European Society of Cardiology and the European Atherosclerosis Society) guidelines recommend that gemfibrozil and statins should not be coprescribed [21, 22].

#### Niacin (Nicotinic Acid)

It is a member of the vitamin B complex and exerts its effects by blocking fatty acid flux from adipose tissue and inhibiting the release of VLDL-c, resulting in reduced TG levels and increased HDL-c levels [23]. This class of drugs causes flushing, leading to discontinuation in many patients. Its use for increasing HDL levels to prevent CHD has not been backed up by current research data.

#### $\omega$ -3 Polyunsaturated Fatty Acids

A number of studies have shown that highly purified  $\omega$ -3 PUFA preparations have a beneficial effect on the lipid profile when used at high doses. Several studies have described the successful use of a statin in combination with  $\omega$ -3 PUFA in patients with mixed dyslipidemia, with a particular benefit observed for TG and VLDL levels [24]. A recent large retrospective 'real world' outcome evaluation involving over 12,000 patients in the UK demonstrated 21% lower all-cause mortality in patients treated with 1 g/day of licensed highly purified  $\omega$ -3 acid ethyl esters within 90 days of a myocardial infarction ( $p < 0.0001$ ) [25]. In South Asians, the intake of  $\omega$ -3 PUFA is low, but it is not clear if  $\omega$ -3 PUFA supplementation would help to ameliorate the metabolic state.

#### *Hypertension*

HTN is one of the major components of MS. Effective treatment of HTN includes achieving a normal BMI in patients who are overweight/obese, adopting a DASH (Dietary Approaches to Stop Hypertension) diet, restricting dietary intake of sodium and regular physical activity along with prescribed pharmacotherapy. Treatment with drugs should be started in patients with BP  $>140/90$  mm Hg in whom lifestyle treatments have not been effective [26]. There are a large number of drugs currently available for reducing BP. Most of the patients require two or more antihypertensive agents selected from different drug classes. These multidrug combinations often produce greater BP reduction at lower doses of the component agents, resulting in fewer side effects [27]. Treatment involves thiazide-type diuretics as initial therapy for most patients, either alone or in combination with one of the other classes (e.g.  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers). If the initial drug selected is not tolerated or is contraindicated, then a drug from one of the other classes proven to reduce cardiovascular events is usually given instead (table 4) [6].

**Table 4.** Treatment/pharmacological modalities and its effect on different MS components

Treatment/drugs	Weight	Blood lipids	Blood glucose	BP
Dietary changes (diet low in calories and fat, high in complex carbohydrates/fibers [28])	+	+	+	+
Physical activity [29]	+	+	+	+
Thiazide-type diuretics [30]	*	-	-	+
$\beta$ -Blockers [30]	-	-	-	+
Angiotensin-converting enzyme inhibitors [30, 31]	$\pm$	$\pm$	$\pm$	+
Angiotensin receptor blockers [30, 32]	$\pm$	$\pm$	$\pm$	+
Calcium channel blockers [30]	$\pm$	$\pm$	$\pm$	+
Metformin [33]	+	$\pm$	+	$\pm$
Glucagon-like-peptide analogues [15]	+	$\pm$	+	$\pm$

+ = Positive effect; - = negative effect;  $\pm$  = insufficient or inconclusive data.

## Conclusions

South Asians are facing growing ‘epidemics’ of obesity and MS. Successful management of obesity includes lifestyle management along with therapeutic interventions. However, some drugs may aggravate other risk factors and therefore need to be used with caution. Evidence is also available for effective intervention programs emphasizing adequate nutrition, physical activity and lifestyle changes starting from childhood for the prevention of obesity, MS and related disorders such as T2DM and dyslipidemia.

## Disclosure Statement

The authors declare no conflict of interest.

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