Review Article

# Management Issues in the Metabolic Syndrome

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## Abstract

The metabolic syndrome or cardiovascular dysmetabolic syndrome is characterized by obesity, central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. The major risk factors leading to this syndrome are physical inactivity and an atherogenic diet and cornerstone clinical feature is abdominal obesity or adiposity. In addition, patients usually have elevated triglycerides, low HDL cholesterol, elevated LDL cholesterol, other abnormal lipid parameters, hypertension, and elevated fasting blood glucose. Impaired fibrinolysis, increased susceptibility to thrombotic events, and raised inflammatory markers are also observed. Given that India has the largest number of subjects with type-2 diabetes in the world it can be extrapolated that this country also has the largest number of patients with the metabolic syndrome. Epidemiological studies confirm a high prevalence. Therapeutic approach involves intervention at a macro-level and control of multiple risk factors using therapeutic lifestyle approaches (diet control and increased physical activity, pharmacotherapy - anti-obesity agents) for control of obesity and visceral obesity, and targeted approach for control of individual risk factors. Pharmacological therapy is a critical step in the management of patients with metabolic syndrome when lifestyle modifications fail to achieve the therapeutic goals. Anti-obesity drugs such as sibutramine and orlistat can be tried to reduce weight and central obesity and jointly control the metabolic syndrome components. Other than weight loss, there is no single best therapy and treatment should consist of treatment of individual components of the metabolic syndrome. Newer drugs such as the endocannabinoid receptor blocker, rimonabant, appear promising in this regard. Atherogenic dyslipidemia should be controlled initially with statins if there is an increase in LDL cholesterol. If there are other lipid abnormalities then combination therapy of statin with fibrates, nicotinic acid, or ezetimibe should be considered. For insulin resistance, drugs such as thiazolidinediones and renin-angiotensin system blockers are available. Available evidence suggests that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may be more beneficial for treatment of hypertension in patients with metabolic syndrome compared to others as these drugs also prevent development of diabetes. Patients with metabolic syndrome also have elevations in fibrinogen and other coagulation factors leading to prothrombotic state and aspirin may be beneficial for primary prevention in these patients. The new developments in the treatment of metabolic syndrome with drugs, such as peroxisome proliferator-activated receptor (PPAR) agonists and cannabinoid receptor-1 antagonists, will broaden the horizons of the current treatment options. Fixed-dose combination polypharmacy using a single pill is an interesting concept that needs to be evaluated in long-term prospective trials in such patients. ©


## Introduction

Multifaceted etiology of cardiovascular diseases, especially coronary heart disease, has been recognized for a long time[1] and clustering of multiple cardiovascular risk factors has been known for at least 80 years. Kylin initially reported that hypertension, hyperglycemia and high uric acid levels in the same individual predicted increased risk of coronary heart disease.[2] The Framingham Study initially described importance of various risk factors for cardiovascular disease and later concluded that multiple risk factors such as smoking, hypertension, and lipid abnormalities were important. Many subsequent prospective studies have confirmed these findings.

Abnormalities of glucose metabolism and diabetes were added to this risk factor conglomerate later. Although insulin resistance in diabetes was reported by Himsworth in 1939 in a series of Goulstonian Lectures to the Royal College of Physicians in London,[3] insulin resistance syndrome as a disease entity was reported in 1988 by Reaven who reported clustering of multiple abnormalities of glucose and lipid metabolism and called it syndrome-X or insulin resistance syndrome.[4] He included insulin resistance, hyperglycemia, hypertension, low HDL cholesterol and high VLDL triglycerides. He surprisingly missed obesity

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or visceral obesity from the definition which was later added as a crucial abnormality. Various names were subsequently proposed the latest being the metabolic syndrome. The cause of the metabolic syndrome remains obscure. Reaven proposed that insulin resistance was the most important abnormality[4,5] while Lemieux et al proposed that visceral obesity and hypertriglyceridemic waist was important.[6] Despite the ongoing arguments among various groups the ultimate importance of this condition is that it helps to identify individuals at high risk of cardiovascular disease.

Several groups have attempted to develop diagnostic criteria for diagnosis of metabolic syndrome.[7] The first attempt was made by a World Health Organization (WHO) diabetes group in 1999 who proposed that insulin resistance or its surrogates, impaired glucose tolerance or diabetes, as essential components and at least two of: raised blood pressure, hypertriglyceridemia and/or low HDL cholesterol, obesity as measured by body-mass index (BMI) or waist-hip ratio (WHR), and microalbuminuria. The European Group for Study of Insulin Resistance in 1999 then produced a modification of the WHO criteria excluding people with diabetes and requiring hyperinsulinemia to be present. Waist circumference was the cutoff for obesity.

A more pragmatic approach was adopted by the US National Cholesterol Education Program: Adult Treatment Panel-3 (ATP-3) in 2001 with a focus on cardiovascular disease risk.[8] The specific objective was to facilitate a clinical diagnosis. It was less glucocentric than earlier definitions and required presence of any three of the five components: central obesity, raised BP, raised triglycerides, low HDL cholesterol and fasting hyperglycemia. There were problems associated with all these three definitions in terms of applicability, uniformity and positive predictive value. A major problem was applicability to different ethnic groups, especially among East Asians and South Asians.[7]

The International Diabetes Federation has recently revised the guidelines to remedy the ethnic group based disparities in the original classification (Table 1).[9] The consensus was that metabolic syndrome as defined the US National Cholesterol Education Program was a pragmatic approach and it was agreed that other definitions unnecessarily highlight diabetes and insulin resistance.[8] Central obesity as assessed by waist circumference was agreed as essential because of the strong evidence linking waist size with multiple metabolic syndrome components. The waist circumference cutoffs were lower for all the ethnic groups. Although this new definition will miss substantial number of subjects with impaired glucose tolerance it retains the simplicity of the US National Cholesterol Education Program's definition. Current opinions have varied to whether metabolic syndrome should be defined to mainly indicate insulin resistance, the metabolic consequences of obesity, risk for cardiovascular disease, or simply a collection of coronary risk factors.[7] We believe in the latter as it is an etiologically heterogenous condition and therapeutically involves multi-pronged approach.

## Management Issues In Metabolic Syndrome

The metabolic syndrome is defined as a condition characterized by a set of clinical criteria: obesity, central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension.[7] The major risk factors leading to the epidemic of this syndrome are physical inactivity and an atherogenic diet and cornerstone of the syndrome is abdominal obesity or adiposity.[10] In addition, patients usually have elevated triglycerides, low HDL cholesterol, elevated LDL cholesterol, other abnormal lipid parameters, hypertension, and elevated fasting blood glucose. Impaired fibrinolysis and increased susceptibility to thrombotic events are also observed in these patients.[7] Recent research also reveals that individuals who have metabolic syndrome have increased levels of inflammatory markers such as, C-reactive protein (CRP) which is now recognized as an important predictor of cardiovascular risk even beyond the known classic risk factors.[11]

In India, both insulin resistance and the metabolic syndrome are widely prevalent.[12-16] The Jaipur Heart

**Table 1 : International diabetes federation metabolic syndrome definition (revised 2005)**

| | |
|---|---|
| Central obesity according to the waist circumference plus any two of following four risk factors. | Ethnic specific<br>South Asians: Men ≥90 cm; Women ≥80 cm<br>Europids: Men ≥94 cm, Women ≥80 cm<br>Chinese: Men ≥90 cm; Women ≥80 cm<br>Japanese: Men ≥85 cm; Women ≥90 cm<br>South and Central Americans: as South Asians |
| Raised triglycerides | ≥150 mg/dl |
| Reduced HDL cholesterol | <40 mg/dl in men<50 mg/dl in women |
| Raised blood pressure | Systolic ≥130 mm Hg<br>Diastolic ≥85 mg/dl<br>Treatment of previously diagnosed hypertension |
| Raised fasting plasma glucose | ≥100 mg/dl<br>Previously diagnosed type 2 diabetes |

Watch Studies have reported that in urban Indian populations age-adjusted prevalence of metabolic syndrome was 18.4%in men and 30.9% in women and 24.9% overall.[15] There is an escalating age-related prevalence in both men and women (Fig.1). Diabetes is already a major epidemic in India and given that India has the largest number of subjects with type-2 diabetes in the world[16] it can be extrapolated that this country would also have the largest number of patients with the metabolic syndrome. Primary care physicians and cardiologists in community practice are on the front lines when it comes to battling the epidemic of metabolic syndrome.[17] The first thing physicians should notice when a patient walks into their examining room is the size of that patient's size and waistline. This is because obesity predisposes individuals to several risk factors that cluster and comprise of the metabolic syndrome.[18]

## Rationale For Aggressive Management Of Metabolic Syndrome

The metabolic syndrome is associated with increased risk of developing both diabetes and cardiovascular disease.[7,17] Risk of diabetes is not surprising as impaired fasting glucose is a component. In the DECODE study involving European men and women subjects with the metabolic syndrome, after exclusion of diabetes, had increased risk of all-cause as well as cardiovascular mortality. The overall hazard ratios for men and women for cardiovascular mortality were 2.26 and 2.78 respectively after adjusting for age, cholesterol and smoking. In three other prospective studies the relative hazard ratios for cardiovascular disease outcomes ranged from 2 to 5. In 10537 NHANES-III participants there was a significant association between prevalent myocardial infarction and stroke and the metabolic syndrome.[7] A series of studies have also found that many middle-aged people with the metabolic syndrome are at increased 10-year absolute risk for cardiovascular disease.[17]

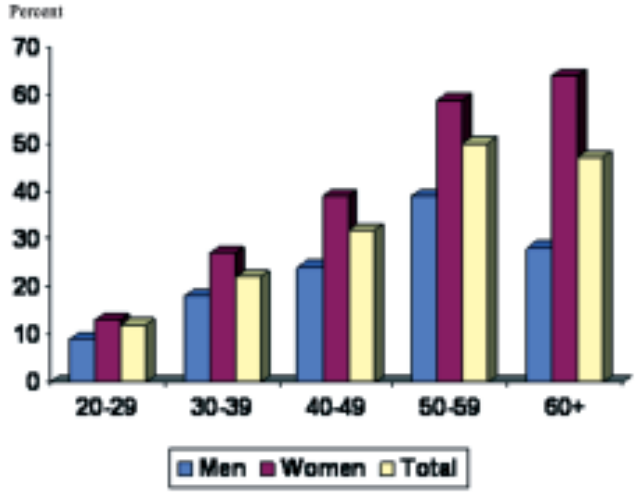


*Fig. 1 : Age-specific prevalence rates of metabolic syndrome (Jaipur Heart Watch-2)[15]*

Individuals with the metabolic syndrome need to be categorized according to absolute 10-year risk. Individuals with overt coronary heart disease, stroke or diabetes are in the high risk category and should be treated accordingly. For other individuals the Framingham risk scoring is advised. This assessment triages subjects into high risk (10 year risk >20%), moderately high risk (10 year risk 10-20%), and moderate risk (10 year risk <10%).[17] These risk calculations include risk factors beyond the metabolic syndrome such as age, sex, smoking, and total cholesterol as these risk factors are important. Studies that estimate the independent influence of metabolic syndrome on Framingham risk scores are still in evolution.

The therapeutic goals for and clinical recommendations for management of metabolic syndrome have been defined (Table 2). These include goals for reducing levels of the abdominal obesity, physical inactivity, atherogenic diet, and smoking. Control of raised blood pressure is crucial. Specific goals for modifying blood levels of LDL cholesterol, triglycerides, and high glucose, and control of proinflammatory and prothrombotic states are suggested. Therapeutic approach involves intervention at a macro-level and control of multiple risk factors using therapeutic lifestyle approaches (diet control and increased physical activity, pharmacotherapy (anti-obesity agents) for control of obesity and visceral obesity, and targeted approach for control of individual risk factors (Table 3).[7,17,22]

## Lifestyle Modification

Non-pharmacologic lifestyle management is important for obesity control.[20,21] In USA it has been reported that 29% of men and 44% of women describe themselves as trying to lose weight. However, restriction of calorie intake and increase in physical activity- the cornerstones of obesity management is reported by only 20%.[20] Many studies demonstrate that obese subjects can lose up to 0.5 kg / week by restricting calories to less than 500-1000 kcal below daily requirements.[21] Although exercise in addition to calorie intake only marginally increases the success of calorie intake program but is associated with many long term benefits. Persons who combine calorie restriction and exercise with behavioral modifications should expect to lose 5-10% of pre-intervention weight over a period of four to six months. This weight loss appears small to the patient but results in improvement of many obesity related conditions including various abnormal components of the metabolic syndrome and development of diabetes.[21]

Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced calorie intake and increased physical activity. Use of principles of behavior change is important. Achievement of target weight loss so as to decrease BMI to less than 23

**Table 2 : Therapeutic goals and clinical recommendations for management of the metabolic syndrome**

| Target | Goal | Recommendations |
|---|---|---|
| Abdominal obesity | 10% weight loss in first year and continued weight loss thereafter. | Diet control and increased physical activity. |
| Physical inactivity | Regular moderate physical activity. | 30-60 minutes of exercise daily. |
| Atherogenic diets | Reduced intake of saturated fats, trans fats and cholesterol. | Total fats 25-35% of total calories, saturated fats <7% of calories. |
| Smoking | Complete cessation. | Complete cessation. |
| High LDL cholesterol | LDL cholesterol <100 mg/dl in moderate risk patients and <70 mg/dl in high-risk patients. | Lifestyle changes and cholesterol lowering drugs to achieve targets. |
| High triglycerides | Insufficient data. Possibly triglycerides <100 mg/dl in high risk patients. | Lifestyle changes and triglyceride lowering drugs (fenofibrate) to achieve targets. |
| Low HDL cholesterol | Insufficient data. | Lifestyle changes and HDL-raising drugs (nicotinic acid, CETP inhibitors) to achieve targets |
| High blood pressure | Blood pressure <135/<85 mm Hg. In diabetes and chronic kidney disease <130/80 mm Hg. | Lifestyle therapy and antihypertensive drugs to achieve targets. |
| Elevated glucose | Reduction and maintenance of fasting glucose <90 mg/dl. HBA1C <7.0% for diabetics. | Lifestyle therapy and hypoglycemic drugs if required. |
| Prothrombotic state | Reduction of prothrombotic state. | Low-dose aspirin in all high and moderate risk patients. Consider clopidogrel if aspirin not tolerated. |
| Proinflammatory state | Reduction of proinflammatory state. | No specific therapies. Aspirin and/or statins are being evaluated. |

**Table 3 : Therapeutic approaches for metabolic syndrome**

| | |
|---|---|
| **Multi-level lifestyle approaches** | Dietary therapy |
| | Physical activity enhancement |
| | Weight reduction |
| **Obesity-specific therapy** | Drugs for weight control |
| | Sibutramine |
| | Orlistat |
| | Cannabinoid receptor blockers |
| | Rimonabant |
| | Surgical approaches |
| | Liposuction |
| | Bariatric surgery |
| **Individual risk factor targeted pharmacotherapy** | Blood pressure control |
| | ACE inhibitors |
| | Angiotensin receptor blockers |
| | Calcium channel blockers |
| | Beta blockers |
| | Alpha blockers |
| | LDL cholesterol reduction |
| | Statins |
| | Statin-ezetimibe and others |
| | Triglyceride reduction |
| | Fibrates |
| | Statins |
| | Statin-fibrate combinations |
| | Omega-3 fatty acids, fish oils |
| | HDL cholesterol enhancement |
| | Niacin |
| | Torcetrapib |
| | Insulin sensitizers |
| | Metformin |
| | Thiazolidinediones |
| | Antithrombotic and anti-inflammatory |
| | Aspirin, clopidogrel |
| | Statins |
| | Hyperglycemia management |
| **Polypharmacy approach** | *Polypill*-like combinations |

**Table 4 : Combination pharmacotherapy for metabolic syndrome and cardiovascular risk reduction**

| **Questions regarding the polypill-concept in metabolic syndrome[76]** |
|---|
| 1. What components should be included in one or more formulations? |
| 2. What can be determined about safety, efficacy and effectiveness using surrogate and hard cardiovascular end points? |
| 3. What characteristics can identify suitable subpopulations for evaluation? |
| 4. Can this therapy be used for primary or secondary prevention? |
| 5. What is the cost-effectiveness of such therapy in primary prevention and secondary prevention in international populations, particularly South Asians? |
| 6. What would be the impact on healthful behaviors and associated prevention programs? |
| 7. What is the role of physicians and other health care workers in advising polypill-like combinations? |

(Asians) or 25 (Caucasians) through lifestyle modifications will reduce most of the constituent risk factors as well as the metabolic syndrome.[7] Both the Finnish Diabetes Prevention Study[23] and the US Diabetes Prevention Program (DPP)[24] showed that diet and exercise had a significant effect on reducing the progression from impaired glucose tolerance to type 2 diabetes. The primary goal in DPP was to prevent or delay the onset of diabetes; the secondary goals were to decrease cardiovascular risk factors, atherosclerosis, and cardiovascular evens. These goals are similar to metabolic syndrome treatment. The DPP enrolled 3234 normotensive mostly obese subjects. The subjects were randomly assigned to intensive lifestyle modification (low energy, low fat diet to induce weight loss with 150

minutes of walking per week), 850 mg of metformin twice daily, 400 mg of troglitazone daily. or placebo. The troglitazone arm was dropped when rare cases of hepatic toxicity were reported from other studies. The remaining treatment groups showed significant differences in rate of development of new diabetes: 11% per year in placebo group, 7.8% in metformin roup (-31%), and 4.8% per year in intensive lifestyle group (-58%). Significantly more patients achieved normoglycemia in lifestyle group as compared to metformin group.[24] These results support use of multiple lifestyle modifications for individuals with the metabolic syndrome.

**Weight reduction and diet intervention**

The available current evidence suggests that the first step in management of patients with metabolic syndrome should be focused weight loss and increased physical activity. The treatment should be based on two major components: behavioral change to reduce caloric intake and an increase in physical activity. A realistic goal for weight reduction should be 7% to 10% over 6 to 12 months. This results in decrease in body weight as well as the insulin resistance.

No particular diet plan or dietary composition has been studied specifically in relation to metabolic syndrome. The current dietary recommendations include a balanced low energy diet containing fruits, vegetables, whole grains, fish and lean meats while minimizing fats, salt, simple sugars, and highly processed foods.[10] The general dietary recommendations include low intake of saturated fats, trans fats and cholesterol, and diets with low glycemic index. Soy protein could be more beneficial than animal protein in weight reduction and correction of dyslipidemia.[17]

Dietary therapies have been studied in relation to atherogenic dyslipidemia that is classical of the metabolic syndrome. Very high carbohydrate intakes can exacerbate this dyslipidemia.[25] If the fat content exceeds 35% of calories it is difficult to sustain the low intakes of saturated fat required to reduce LDL cholesterol. On the other hand if the fat content falls below 25%, triglycerides can rise and HDL cholesterol levels tend to decline. To avoid worsening of atherogenic dyslipidemia some investigators favor fat intakes in the range of 30-35% and most prefer fat intakes of 25-30% to avoid weight gain.[17]

Other weight reducing diets such as high-protein low-carbohydrate diets have recently come into vogue. Research documenting the benefits of such high fat / high protein / low calorie diets is lacking. Stern et al reported that after one year of consumption of low-carbohydrate diet, severely obese patients showed no more weight reduction than those eating a conventional weight loss diet.[25] A study comparing four types of weight reducing diets (Atkins, Ornish, Weight Watchers and Zone diets) reported no particular benefit of any particular diet on weight loss at one year.[26] Dansinger et al randomized 160 individuals to the four diet programs. Overall adherence to any particular program was low and it was reported that at the end of one year the adherence was only 2-3 points on a 10 point scale. The diets resulted in a significant reduction in LDL cholesterol but no change was observed in blood pressure and glucose levels despite a significant weight loss (-2.1 to -3.2 kg weight, -0.7 to -1.4 kg / $m^2$ BMI) in all the groups. Weight loss was associated with decline in fasting insulin levels and total / HDL cholesterol. Thus it is clear that weight loss rather than the diet type is more important in ameliorating the risk factors of the metabolic syndrome.

**Physical activity**

The DPP study showed that multiple metabolic risk factors can be controlled and type 2 diabetes prevented or delayed by keeping weight in control by increasing physical activity.[27,28] The study found that the participants who increased their physical activity and lost 5-7% of their body weight (5-10 kg) reduced their progression to diabetes by 58% during the course of the study.[28] Physical activity is associated with successful weight reduction and these therapeutic lifestyle changes can reduce by half the progression to new-onset diabetes in patients with metabolic syndrome.[17] It also reduces overall cardiovascular risk. Physical activity recommendations should include practical, regular, and moderated regimens of exercise, with a daily minimum of 30 to 60 minutes. More exercise adds more benefit. Regular exercise also improves endothelial function and vascular health. Sixty minutes or more of continuous or intermittent aerobic activity, preferably done every day will promote weight loss and weight maintenance. The latter include multiple short (10-15 minute) bouts of activity (walking breaks at work, gardening or household work), jogging, swimming, biking, golfing, or team sports. An equal balance between aerobic exercise and strength training is advised.

**Yoga interventions**

Important issues in lifestyle management include behavior modification through counseling and adherence promoting techniques. Use of traditional Indian systems such as yoga and transcendental meditation can be important adjunct to lifestyle changes and promote compliance. The Lifestyle Heart Study by Ornish et al[29] was the first randomized trial demonstrating usefulness of comprehensive lifestyle changes along with certain yogic practices in ameliorating multiple cardiovascular risk factors (now known as metabolic syndrome) and causing regression of coronary atherosclerosis. In a randomized study in 48 patients it was demonstrated that strict dietary control (<10% calories as fat), regular exercises and meditation resulted in significant decrease in weight and various risk factors associated with the metabolic syndrome. Amelioration of multiple cardiovascular risk factors has

been demonstrated in other studies that have evaluated a similar comprehensive lifestyle modification program including yoga,[29-32] for example, Manchanda et al[31] reported significant improvement in multiple metabolic risk factors and regression of coronary atherosclerosis using a comprehensive lifestyle change package that included diet control, physical activity and yoga techniques.

Thus, it is clear that a comprehensive approach consisting of weight reduction, regular physical exercise and yoga is crucial in control of the insulin resistance state that characterizes the metabolic syndrome.

## PHARMACOLOGICAL TREATMENT

Pharmacological therapy is a critical step in the management of patients with metabolic syndrome when lifestyle modifications fail to achieve the therapeutic goals (Table 2). Anti-obesity drugs such as sibutramine and orlistat can be tried to reduce weight and central obesity and jointly control the metabolic syndrome components. Other than weight loss, there is no single best therapy and treatment should consist of treatment of individual components of the metabolic syndrome. Newer drugs such as the endocannabinoid receptor blocker, rimonabant, appear promising in this regard. Atherogenic dyslipidemia should be controlled initially with statins if there is an increase in low-density lipoprotein (LDL) cholesterol. If there are other abnormalities, combination therapy, including fibrates, nicotinic acid, or ezetimibe should be considered. For insulin resistance, drugs such as thiazolidinediones and renin-angiotensin system blockers are available.[7,17] Available evidence suggests that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may be more beneficial for treatment of hypertension in patients with metabolic syndrome compared to others as these drugs also prevent development of diabetes.[33] Large randomized clinical studies of ACE inhibitors and ARBs have shown that ACE inhibitors reduce the incidence of diabetes by 14% to 34% and ARBs reduced the incidence of diabetes by 19% to 25%.[34] The mechanisms by which this effect takes place is not clear and a putative mechanism is a differential effect of ACE inhibition on insulin sensitivity and glucose tolerance. Patients with metabolic syndrome also have elevations in fibrinogen and other coagulation factors leading to prothrombotic state and aspirin may be beneficial for primary prevention in these patients.[7] The new developments in the treatment of metabolic syndrome with drugs, such as peroxisome proliferator-activated receptor (PPAR) agonists and cannabinoid receptor-1 antagonists, will broaden the horizons of the current treatment options. Fixed-dose combination polypharmacy using a single pill is an interesting concept that needs to be evaluated in long-term prospective trials in such patients.

### Obesity Management

#### *Sibutramine and Orlistat*

Currently available weight loss drugs possess limited utility in the management of obesity but maybe useful in some patients. Krejs reported that sibutramine-induced weight loss and weight maintenance lead to clinically relevant reductions in risk factors associated with the metabolic syndrome.[35] Treatment with the drug decreases visceral fat, improves lipid levels, decreases glycosylated haemoglobin and decreases uric acid concentrations. In the ORACARDIA study, 126 subjects with criteria fulfilling metabolic syndrome were evaluated, 94 on orlistat and 34 on a hypocaloric diet.[36] At the end of six months of intervention, 91% patients in control group had some evidence of the metabolic syndrome as compared to 65% in orlistat group ($p<0.0001$). Hseih et al performed a randomized controlled trial in Taiwan involving 51 patients on orlistat 360 mg/day and 55 control subjects.[37] The orlistat group had greater changes in body mass index (BMI), % body fat, waist circumference, and insulin resistance, C-reactive protein (CRP), leptin and adiponectin levels after one year on the program as compared to the controls. It was concluded that orlistat could effectively manage obesity related co-morbidities, especially insulin resistance and atherosclerosis risk. Another study with orlistat, XENDOS, has also reported benefits of orlistat in association with lifestyle changes in prevention of type 2 diabetes in patients at high risk.[38] However, the major problem with these currently available anti-obesity drugs is a relatively high rate of adverse side effects leading to poor tolerance and compliance for long term use.

#### *Cannabinoid$_1$ receptor ($CB_1$) antagonists*

Rimonabant belongs to a new class of drugs which selectively antagonize cannabinoid type 1 receptors ($CB_1$).[39] This novel class of drugs has been reported to be useful in reduction in bodyweight along with a parallel decrease in waist circumference and amelioration of the metabolic profile.[40] In the RIO-Europe study 1507 patients with BMI $\geq$30 kg/m$^2$ or BMI $\geq$27 kg/m$^2$ with dyslipidemia, hypertension or both were randomized to receive double blind treatment with placebo, 5 mg rimonabant, or 20 mg rimonabant once daily in addition to a mild hypocaloric diet. Weight loss was significantly greater in the rimonabant groups as compared to controls. Those on 20 mg/day of the drug also showed significantly greater improvements than placebo in waist circumference, high density lipoprotein (HDL) cholesterol, triglycerides, insulin resistance and prevalence of the metabolic syndrome. It was also observed that in addition to its effects on weight loss rimonabant had significant weight independent effect on lipid parameters.[40] Rimonabant also reduced fasting insulin levels, glucose and CRP.

The RIO-Lipid study examined the effects of rimonabant on metabolic risk factors, including

adiponectin levels, in high-risk patients who are overweight or obese and have dyslipidemia.[41] 1036 overweight or obese patients (BMI 27-40) with untreated dyslipidemia (high triglyceride levels or cholesterol:HDL ratio >4.5 among women and >5 among men) were randomized to double-blinded therapy with either placebo or rimonabant at a dose of 5 mg or 20 mg daily for 12 months in addition to a hypocaloric diet. The rates of completion of the study were 62.6 percent, 60.3 percent, and 63.9 percent in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively. The most frequent adverse events resulting in discontinuation of the drug were depression, anxiety, and nausea. As compared with placebo, rimonabant at a dose of 20 mg was associated with a significant (P<0.001) mean weight loss (-6.7±0.5 kg), reduction in waist circumference (-5.8±0.5 cm), increase in HDL cholesterol (+10.0±1.6 percent), and reduction in triglycerides (-13.0±3.5 percent). Rimonabant at a dose of 20 mg also resulted in an increase in plasma adiponectin levels (57.7 percent, P<0.001).It was concluded that rimonabant significantly reduces body weight and waist circumference and improves the profile of several metabolic risk factors in high-risk patients who are overweight or obese and have an atherogenic dyslipidemia.

In RIO-North America study[42] 3045 obese subjects were randomized into placebo group and to rimonabant 5 mg and 20mg. At year 1, the completion rate was 309 (51%) patients in the placebo group, 620 (51%) patients in the 5 mg of rimonabant group, and 673 (55%) patients in the 20 mg of rimonabant group. Compared with the placebo group, the 20 mg of rimonabant group produced significantly greater mean reductions in weight (–6.3 vs –1.6 kg), waist circumference (–6.1 vs –2.5 cm), and level of triglycerides (percentage change, –5.3 vs 7.9) and a greater increase in level of HDL cholesterol (percentage change, 12.6 vs 5.4) (p<0.001). Patients who were switched from the 20 mg of rimonabant group to the placebo group during year 2 experienced weight regain while those who continued to receive 20 mg of rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors. More ongoing clinical and mechanistic trials shall be able to answer questions regarding risk/benefits and pharmacogenomics of this class of drugs.

***Surgical management of obesity***

Liposuction or bariatric surgery are being used for severe obesity in many developed countries.[43] In a randomized trial of liposuction it was reported that despite a significant weight loss there was no influence on lipid profile or other parameters of the metabolic syndrome. Klein et al studied 15 obese women and evaluated insulin sensitivity of liver, skeletal muscle and adipose tissue as well as inflammatory mediators and other cardiovascular risk factors before and 10-12 weeks after the liposuction procedure.[44] Liposuction decreased the volume of subcutaneous abdominal adipose tissue by 28-44% and subjects lost 9-10 kg of fat. However, liposuction did not alter the insulin sensitivity of muscle, liver or adipose tissue and also did not alter plasma concentrations of CRP, interleukin-6 or TNF-alpha and no change was observed in other coronary risk factors such as lipid levels and blood pressure.

Bariatric surgery techniques using laparoscopic adjustable banding of stomach along with Roux-en-Y and other forms of gastric bypass are now favored for severe and morbid obesity.[7] It results in weight loss of 25-30% and rapid normalization of glucose handling and blood pressure in patients with diabetes and hypertension.[45] Long-term results are however not available and recent reports of substantial mortality and morbidity of this procedure, especially in the elderly have raised important safety issues for this procedure.[46]

**Individual Risk Factor Modification**

A recent American Heart Association and National Heart Lung Blood Institute scientific statement highlights the importance of control of individual risk factors in metabolic syndrome.[17] This consensus group considers metabolic syndrome as a clustering of risk factors that increase the cardiovascular event risk and suggests a multipronged therapeutic approach. Components of the metabolic control that need control are atherogenic dyslipidemia, elevated blood pressure, elevated fasting glucose, prothrombotic factors, and proinflammatory state.

**Lipid management**

The lipid abnormalities in the metabolic syndrome have been described as atherogenic dyslipidemia. This definition was initially proposed by Grundy and included borderline high LDL cholesterol and apolipoprotein B, increased small dense LDL particles, raised triglycerides and low HDL cholesterol levels.[47] A major debate in the field of lipids is whether the therapeutic approach should focus exclusively on LDL cholesterol reduction or it should be directed at improvements in LDL cholesterol, triglycerides, and HDL cholesterol simultaneously. The ATP-III guidelines emphasize that LDL reduction is the primary target in lipid management even in the metabolic syndrome and low HDL and triglycerides are secondary targets.[8] Canadian guidelines have adopted both a LDL cholesterol goal of <100 mg/dl and a total/HDL cholesterol ratio of <4.0.[48] In keeping with these recommendations, we would suggest that LDL cholesterol should be lowered to less than 70 mg/dl in all high risk cases with the metabolic syndrome. This recommendation is supported by the recent TNT-Metabolic syndrome study that showed greater reduction in coronary events in the group that achieved LDL cholesterol levels of 70 mg/dl than group with LDL levels of about 100 mg/dl.[49]

### *Statins*

The efficacy of statins in reducing LDL cholesterol concentrations is well established. Studies show that statins appear to improve the LDL subfraction profile, possibly by reduction of small dense LDL or by reduction in all LDL subclasses with a shift in LDL particle distribution.[50] LDL targets have been defined by various agencies according to the level of cardiovascular risk. In moderate risk subjects the target is <100 mg / dl while in high risk subjects it is <70 mg / dl.[44] The target LDL levels in patients with the metabolic syndrome are difficult to achieve by diet or exercise therapy alone and usually need drug therapy, usually a statin. This class of drugs also reduces all apolipoprotein B containing lipoproteins and also decreases concentration of CRP.

Combination therapy for dyslipidemias has been suggested for achieving target LDL and other lipid levels.[51] This is akin to treatment of hypertension and diabetes where usually two or likely three drugs are required to achieve target levels of control. Ezetimibe is a novel cholesterol lowering agent and studies report when combined with any statin in a dose of 10 mg daily was as effective as the statin monotherapy as the highest dose, e.g., ezetimibe plus 10 mg atorvastatin was as effective as 80 mg atorvastatin alone. This combination was also more effective that statin alone in reducing triglycerides and apolipoprotein B (ApoB) and in increasing HDL cholesterol. Statins can also be safely combined with a fibrate, especially fenofibrate, and niacin to achieve target levels of non-HDL cholesterol, triglycerides and HDL cholesterol.[8,51]

### *Fibrates*

Fibrates mitigate atherogenic dyslipidemia and are useful in dyslipidemia of the metabolic syndrome. In combination with statins they are particularly effective for reducing LDL cholesterol as well as triglycerides. However the combination therapy carries some increased risk for myopathy. The myopathy has been specially noted with statin and gemfibrozil combination due to pharmacological interaction of statin glucuronidation and increase in level of statins when used in conjunction. The risk of myopathy is very low when fenofibrate is combined with a statin and the ATP-III has recommended this combination.[8]

Both statins and fibrates have demonstrated a capacity to reduce primary and secondary cardiovascular event rates in prospective placebo-controlled trials. Clinical trial data with statin-fibrate combination are quite limited. In the Fluvastatin Alone and in Combination Treatment (FACT) Study, 20 or 40 mg of fluvastatin daily was used in combination with 400 mg bezafibrate in 167 patients with mixed dyslipidemia over a 6-month follow-up period. Combination therapy was superior and mean changes in lipoproteins from baseline to end-point included a 22% increase in HDL cholesterol levels and reductions of 24% and 38% in LDL cholesterol and triglycerides respectively.[52] Combination therapy was not associated with increased risk of myopathy or hepatotoxicity. An outcome trial with statin-fibrate therapy is yet to be completed but one is underway: the Action to Control Cardiovascular Risk in Diabetes trial. This trial is assessing the safety and efficacy of statin monotherapy alone as compared to statin-fibrate combination in 5800 patients with diabetes and is expected to be completed by the year 2009.

Fibric acid is a synthetic ligand of the nuclear receptor PPAR-$\alpha$ and promotes oxidation of fatty acids to mediate hypolipidemic action.[53] PPAR-$\alpha$ exerts direct antiatherogenic action on the vessel wall and improves endothelial function. Endothelial dysfunction in the metabolic syndrome is characterized by an impaired insulin stimulated nitric oxide production from the endothelium and decreased blood flow to skeletal muscle. Fibrates, therefore, may have an action beyond the hypolipidemic action to decrease the incidence of coronary artery disease. However the results of the fenofibrate intervention and event lowering in diabetes (FIELD) study do not confirm the usefulness of fibrates in primary cardiovascular prevention.[54] In this multinational randomized controlled trial 9795 participants aged 50-75 years with type 2 diabetes were evaluated using micronised fenofibrate 200 mg daily (n=4895) or matching placebo (n=4900). After an average follow-up of 5 years, fenofibrate did not significantly reduce the risk of primary outcome of coronary event. It did reduce total cardiovascular event mainly due to fewer non-fatal myocardial infarctions and revascularizations. The authors opined that a high rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit. This study questions the usefulness of fenofibrate and other fibrates in primary prevention of cardiovascular events in high risk subjects with diabetes or cardiovascular diseases and has implications for use of fibrates in metabolic syndrome.

### *Niacin*

Niacin raises HDL cholesterol levels and reduces non-HDL cholesterol. Patients with impaired fasting glucose, impaired glucose tolerance or diabetes who are treated with nicotinic acid deserve careful monitoring for worsening hyperglycemia.[8] Lower doses of niacin decrease this risk. The combination of a statin with a low dose of niacin is a very attractive option in patients with metabolic syndrome. This combination has been reported to lower LDL cholesterol, ApoB, triglycerides and lipoprotein(a) and increase HDL cholesterol significantly in an Indian multicentric study.[55] In this open-label study, 142 patients with mixed dyslipidemia and LDL cholesterol $\geq$130 mg / dl were treated with lovastatin (20 mg) and extended release niacin (375 mg) per day. In the study percent decline in various lipids at

4, 12 and 24 weeks was: total cholesterol 11.8, 18.8 and 25.2%, LDL cholesterol 17.0, 28.8 and 38.0%, triglyceride 6.8,12.8 and 21.0%, lipoprotein(a) 17.5 , 26.9 and 44.5% respectively ($p<0.01$). HDL cholesterol and apoA1 / apoB increased by 7.2, 13.1 and 18.2%; and 7.9, 21.9 and 51.6% respectively ($p<0.01$). Target LDL levels (<100 mg / dl in subjects with manifest coronary heart disease or diabetes; <130 mg / dl in subjects with >2 risk factors) were achieved in 92 (80.7%) patients. 13 patients (10%) were lost to follow-up and 4 (3%) withdrew because of dermatological adverse effects- flushing. pruritus and rash. This study showed that low dose niacin is useful treatment of mixed dyslipidemia as is present in the metabolic syndrome.

***Omega-3 fatty acids***

Fish oils (omega-3 fatty acids) have been studied in trials after myocardial infarction and have been shown to reduce cardiovascular events and death. They are activators of PPAR-$\alpha$ system. Fish oils have been used in patients with diabetes and metabolic syndrome who need additional triglyceride lowering.[17] In metabolic syndrome patients, 3 gm of fish oils have been shown to decrease triglycerides by 20%, decrease in ApoB production, decrease in postprandial lipemia and marked reduction in small dense LDL. Extremely high doses should be avoided to prevent increase in LDL cholesterol levels.

***HDL cholesterol modulation***

A number of strategies for increasing HDL cholesterol are under evaluation. These include cholesterol ester transfer protein (CETP) inhibition, increasing ApoA1 (ApoA1Milano), inhibitors of acyl coenzyme A-cholesterol acyltransferase (ACAT), and others.[56] Inhibitors of CETP have been shown to increase HDL cholesterol significantly and a study with this novel class of drugs using torcetrapib reported almost 100% increase in HDL cholesterol levels in a controlled study.[57] Brouseau et al conducted a single-blind placebo-controlled study to examine the effects of torcetrapib in 19 subjects with low HDL cholesterol (<40 mg / dl), 9 of whom were also treated with atorvastatin 20 mg daily. Treatment with torcetrapib 120 mg daily for four weeks increased HDL cholesterol by 61% and 46% respectively in atorvastatin and non-atorvastatin cohorts and with 120 mg twice daily increased it by 106% in both cohorts ($p<0.001$). It was concluded that torcetrapib was effective in increasing HDL cholesterol levels significantly. The effect of these inhibitors on atherosclerosis progression as well as clinical significance needs to be evaluated in larger clinical trials.[58]

**Elevated blood pressure**

The pathophysiological mechanisms by which hypertension is linked so strongly with obesity, particularly central obesity and hyperinsulinemia remain uncertain. There have been two enduring hypotheses; the first considers that sympathetic system underactivity is present in obesity and through consequential failed stimulation of thermogenesis provides a metabolic basis for the obesity and second consider that in obesity sympathetic nervous system over-activation occurs with chronic overeating where it facilitates energy balance and weight stabilization, but at the cost of adverse consequences attributable to chronic sympathetic stimulation, in particular, elevation in blood pressure.[59]

Lifestyle changes are of prime importance to reduce elevated blood pressure with a goal to reduce it as much as possible, ideally >130 / 85 mm Hg or even >120 / 80 mm Hg. Lifestyle therapies include weight control, increased physical activity, decreased intake of alcohol, sodium restriction and increased consumption of fresh fruits and vegetables as in the dietary approaches to stop hypertension (DASH) diet.[60] If hypertension cannot be adequately controlled by lifestyle therapies, antihypertensive drug therapies are usually necessary to prevent long term adverse effects. Whether findings of neural pathophysiology of obesity- and central obesity-related hypertension have any implications for defining pharmacological treatment is not clear. Sympathetic activation in obese hypertensive patients seems to contribute both to elevated blood pressure as well as cardiovascular and metabolic consequences of the metabolic syndrome and it is theorized that drugs inhibiting the sympathetic nervous system could be useful but the evidence of efficacy of central imidazoline-receptor binding agents and peripheral beta-adrenergic blocking agents is not convincing. A diabetogenic effect has been unequivocally demonstrated for both thiazide diuretics and beta-blockers and at present these drugs may not be suitable first line therapy in subjects with metabolic syndrome.

***ACE inhibitors***

An increasing number of experts support ACE inhibitors as first line therapy in the metabolic syndrome, especially when type 2 diabetes or renal disease is present.[34,60] Inhibition of renin-angiotensin system with this class of drugs may lower the risk of diabetes itself as reported in large randomized clinical studies of ACE inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitors reduced the incidence of diabetes by 14-34% and ARBs reduced the incidence of diabetes by 19-25%.[34] The mechanisms of action of ACE inhibitors or ARBs are not clear and a possible mechanism is improvement in insulin sensitivity and glucose tolerance. Angiotensin II interferes with postreceptor insulin signaling and blocking of this action enhance insulin sensitivity. This group of drugs also reduces inflammation. In addition these drugs reduce oxidative stress and also improve endothelial function which would enhance glucose utilization by skeletal muscle due to increased delivery secondary to improved flow.

Small mechanistic studies report that within 2-12 weeks of therapy with ACE inhibitors the insulin sensitivity improves. ARBs may be used when ACE inhibitors are not tolerated and have similar beneficial effects in prevention of diabetes.[61] However, tailoring of antihypertensive therapy to pathophysiology cannot be presently the prime therapeutic principle because of the imperfect knowledge. Clinical considerations such as the presence of coexisting illnesses are important in drug selection. In general, most experts agree that a drug that blocks renin-angiotensin system should be one of the initial therapeutic choice.

**Insulin resistance, fasting hyperglycemia, and impaired glucose tolerance**

Insulin resistance and hyperinsulinemia are associated with multiple metabolic abnormalities that are present in the metabolic syndrome.[7] These include (a) some degree of glucose intolerance, (b) dyslipidemia-raised triglycerides, low HDL cholesterol, small dense LDL particle diameter and postprandial lipemia, (c) sympathetic nervous system overactivity, renal sodium retention and hypertension, (d) abnormal uric acid metabolism with raised plasma uric acid concentrations and decreased renal uric acid clearance, (e) abnormal hemostasis and raised fibrinogen and plasminogen activator inhibitor-1, (f) inflammatory milieu with raised white cell count and CRP, and (g) endothelial dysfunction. Decreasing the raised insulin levels by lifestyle changes and pharmacotherapy can revert many of these abnormalities.

***Lifestyle changes***

An attractive option in treatment of the metabolic syndrome might be to begin treatment in individuals with impaired fasting glucose or impaired glucose tolerance before overt hyperglycemia develops. Results of recent studies indicate that targeting these individuals with dysglycemia using aggressive lifestyle interventions or pharmacotherapy can reduce the incidence of diabetes and might reduce the cardiovascular risk. Influence of lifestyle interventions have been reported above. The Finnish Diabetes Prevention Study[23] and the US-DPP[24,27,28] showed that diet and exercise had a significant effect on reducing the progression from impaired glucose tolerance to type 2 diabetes. In the Finnish study and the DPP personalized recommendations about diet and exercise reduced incidence of new onset diabetes by 58% compared to the group receiving usual instructions. Similar results have been obtained in the Malmo study[62,63] and the Da Qing trial[64]. Diet and exercise in the Malmo study reduced diabetes incidence by 50% and at 12 year follow-up the group that achieved normoglycemia had similar mortality as normal subjects.[63] The Da Qing trial demonstrated that diet alone, exercise alone or their combination significantly reduced the incidence of diabetes.[64]

***Metformin***

Metformin combined with standard lifestyle advice was one of the treatments evaluated in DPP.[24] Although metformin was effective in reducing the incidence of diabetes as compared with placebo (31% reduction, $p<0.01$), it was not as effective as intensive lifestyle intervention. Metformin was less effective than lifestyle changes in improving cardiovascular risk factors.[65] More studies are required with metformin in the context of metabolic syndrome.

***Acarbose***

Acarbose, an inhibitor of $\alpha$-glucosidase slows the digestion of carbohydrates in the intestine and reduced postprandial glucose levels. The Study to Prevent Non-Insulin Dependent Mellitus (STOP-NIDDM) was a randomized trial to evaluate whether acarbose would prevent development of type 2 in subjects with impaired glucose tolerance.[66] In the acarbose group as compared to placebo group significantly less developed diabetes (32% vs 42%, $p=0.0015$) and probability of reverting to normal glucose tolerance was significantly greater. There was also a reduction in risk of developing cardiovascular events.

***PPAR-$\alpha$ and PPAR-$\gamma$ agonists***

Thiazolidinedione drugs such as troglitazone, rosiglitazone and pioglitazone enhance insulin sensitivity. In an early randomized study with troglitazone (now withdrawn) in 266 Hispanic women with post gestational diabetes, it was found to reduce incidence of diabetes by 55% ($p=0.009$) and also to alter the natural course of diabetes.[67] Troglitazone has also been studied in the DPP and patients with impaired glucose tolerance and have been shown to be effective in prevention of diabetes but have not been demonstrated to reduce cardiovascular risk.[27] Pioglitazone has been shown to reduce multiple components of metabolic syndrome such as high blood pressure, high blood glucose and triglycerides in addition to a decrease in urinary albumin / creatinine ratio.[68]

The PROACTIVE study evaluated secondary prevention of macrovascular events in patients with type 2 diabetes using pioglitazone in a randomized controlled trial.[69] These investigators evaluated 5238 patients with type 2 diabetes who had evidence of macrovascular disease at baseline and randomized 2605 subjects to 15 to 45 mg of pioglitazone and 2633 to placebo. Primary endpoint was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in coronary or leg arteries, and above-ankle amputation. The composite endpoint was not significantly different in the two groups but pioglitazone reduced composite of all-cause mortality, non-fatal myocardial infarction and stroke (hazard ratio 0.84, confidence intervals 0.72-0.89, $p=0.027$). It was concluded that pioglitazone may be useful in prevention

of cardiovascular events in high risk patients with type 2 diabetes although the usefulness of this approach in metabolic syndrome or impaired glucose tolerance subjects is not clear. However, use of this group of drugs has not been recommended for treatment of metabolic syndrome by a consensus group.[17]

Preclinical trials with dual PPAR blockade have shown promising results in ameliorating insulin resistance and diabetic hyperglycemia.[70] Cardiovascular risk factor improvements have to be confirmed in clinical trial setting. Combination therapy of PPAR blockade with other strategies is also being evaluated. There are three major trials using combination therapies currently in progress examining the effect of rosiglitazone / ramipril (the DREAM study), nateglinide / valsartan (the NAVIGATOR study) and pioglitazone (the ACT-NOW study) on the development of diabetes in impaired glucose tolerance subjects as a primary outcome. There are studies for prevention of diabetes as secondary outcomes of which the ONTARGET-TRANSCEND study is examining telmisartan with or without ramipril in a very large study. The evidence is overwhelming: progression of insulin resistance to diabetes can be prevented or delayed in high risk population through lifestyle modification and / or pharmacological interventions.

***Early insulin therapy***

An interesting hypothesis is of prevention of β-cell fatigue in context of insulin resistance. The ORIGIN study is testing glargine insulin in patients with impaired glucose tolerance.[71] The ORIGIN is a large, international, multicentre trial investigating in high risk people with impaired glucose tolerance or early diabetes, whether insulin replacement therapy targeting fasting normoglycaemia with insulin glargine reduces the risk of long-term cardiovascular events more than standard approaches to dysglycaemia. The study commenced in 2003 and is expected to conclude in the year 2009.

**Prothrombotic and proinflammatory state**

Subjects with the metabolic syndrome have increased levels of fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and other coagulation factors. They also have a proinflammatory state characterized by elevated cytokines- tumor necrosis factor and interleukin-6, and acute phase reactants such as CRP and fibrinogen. For primary prevention the only long–term approach to counter the thrombotic state is low dose aspirin or other anti-platelet agents.[7,17] Aspirin is widely recommended in patients with established cardiovascular diseases although its role in prevention of events in diabetes is not well established. In metabolic syndrome patients with a high risk of future cardiovascular events, aspirin in a dose of 75-150 mg / day is an attractive therapeutic option to lower vascular events.[72] It is also important to note that renin-angiotensin system inhibition also reduces PAI-1 levels and inflammatory cytokines and thus potentially reduces risk of increased thrombotic events in patients with metabolic syndrome.[34]

An elevated CRP level of >3 mg / dl (in absence of other detectable causes) is a useful marker of proinflammatory state. Finding of an elevated level supports the need for lifestyle changes. Weight reduction leads to a decrease in CRP levels and also mitigates other inflammatory factors. No drugs that act exclusively via this mechanism are available for reducing cardiovascular risk. However, several drugs used to treat other metabolic risk factors in the metabolic syndrome have been reported to reduce CRP levels. These drugs groups are statins, nicotinic acid, fibrates, ACE inhibitors or ARBs, and thiazolidinediones but isolated regular use of these drugs to reduce the inflammatory markers has not yet been demonstrated to result in improved clinical outcomes.

**Polypharmacological Approach**

Wald and Law have suggested a polypharmacy concept to prevent cardiovascular disease.[73] A combination "polypill" has been suggested that contains three antihypertensives (thiazide, beta-blocker and ACE inhibitor), a statin, aspirin, and folic acid in low doses based on current clinical evidence. It has been hypothesized that such a combination if given to everyone more than 55 years of age in Britain would prevent 88% (84-91%) of heart attacks and 80% (71-87%) strokes. This combination highlights the need for multifactorial interventions in prevention of cardiovascular diseases and underscores the clinical importance of the metabolic syndrome. Such a combination approach has yet to be formally evaluated although a retrospective analysis has reported significant benefits. In a British general practice open prospective cohort evaluation of 1.18 million patients and using a nested case-control design, 2266 incident coronary heart disease death cases were matched to 9064 controls.[74] It was observed that a combination of aspirin, statin and beta-blocker improves survival. Drug combinations associated with the greatest reduction in all cause mortality were statins, aspirin and beta blockers (-83%) while a combination of statin, aspirin, beta blocker and ACE inhibitor reduced mortality by 75%. Economic issues in such a combination therapy in developing countries should be resolved as polypharmacy can lead to a massive burden.[75]

The use of combination pharmacotherapy as suggested by the polypill authors has been reviewed by a US expert panel.[76] It was concluded that the combination therapy as suggested by Wald and Law may prove to be effective but may also have side effects and poor adherence, which may be greater or lesser than other preventive approaches. It has also been suggested that randomized trials are needed to evaluate this therapy although the study design is uncertain. Minority groups and people with low socioeconomic status in

the US may be especially suitable for such therapies given the high prevalence of obesity and related cardiovascular risk factors in these groups but a large number of questions need to be answered in this context (Table 3).

We believe that the polypill concept is especially suitable for the management of metabolic syndrome. The issues to be addressed include the evidence-based use of such a combination pill in primary or secondary prevention and cost-effectiveness and assessment of its impact on cardiovascular healthful behaviors. Such combinations (2, 3 and 4 drug combos) are already available in India and some other developing countries but issues related to long-term safety and benefits needs to be addressed in a properly designed multifactorial randomized clinical trials. Ethical issues involved also need to be clarified before undertaking such a study.

## Conclusions

The metabolic syndrome is an important public health problem in South Asians in their homeland and worldwide. It has also emerged as an important issue in developed countries. This epidemic has been fuelled by escalating epidemic of obesity. A strong correlation of various measures of obesity (adiposity) such as body mass index, waist size and waist hip ratio with various components of the metabolic syndrome is observed in Indian studies[19] showing that obesity management and weight optimization should be the primary target of therapy in these individuals.

Lifestyle interventions are crucial in this regard. Interventions targeted to reduce obesity and adiposity are effective in reducing overall cardiovascular risk and positively modify the metabolic syndrome parameters. Increased physical activity is the single most useful intervention to modify global cardiovascular risk by affecting all the components of the metabolic syndrome (obesity, atherogenic dyslipidemia, insulin resistance and high blood pressure). Diet modification and control leads to control of obesity, lipids and blood pressure. Yoga-based interventions can have positive influences on mind-body relationships and improve compliance to lifestyle changes.

Pharmacological interventions to specifically target all the risk factors are limited. Obesity modulation offers the best strategy and newer drugs such as the novel cannabinoid receptor blocking agent, rimonabant, offers much promise as it improves most of the components of metabolic syndrome. Focus on individual risk factor modification involves a multipronged strategy to control borderline high LDL cholesterol (statins, statin-ezetimibe combination), high triglycerides (fibrates, fibrate-statin combination, omega-3 fatty acids), low HDL cholesterol (niacin, fibrates, torcetrapib, ApoA1 Milano), high blood pressure (ACE inhibitors, ARBs, β-blockers, and others), and insulin resistance (metformin, acarbose, thiazolidinediones). Combination polypharmacy and use of polypill-like combinations is an attractive option in control of the overall risk factors of the metabolic syndrome. This strategy needs to be formally evaluated in settings of randomized controlled trials. Until that time population based lifestyle interventions are crucial and best evidence-based approaches in South Asian populations.[76,77] The time has come to aggressively market cardiovascular and other chronic diseases prevention strategies in India and other developing countries.

## References


1. Stamler J. Established major coronary risk factors: historical overview. In: Marmot M, Elliot P. Eds. *Coronary heart disease epidemiology: from aetiology to public health.* 2nd Ed. Oxford. Oxford University Press. 2005;18-31.
2. Kylin E. Studien uber das hypertonie-hyperglykamie-hyperurikamie syndrome. *Zentralblatt fur Innere Medizin* 1923;44:105-27.
3. Himsworth HP. The mechanism of diabetes mellitus. *Lancet* 1939; ii:1-6.
4. Reaven G. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-1607.
5. Reaven G. Insulin resistance, type 2 diabetes and cardiovascular disease: the end of the beginning. *Circulation* 2005;112:3030-32.
6. Lemieux I, Pascot A, Couillard C, et al. Hypertriglyceridemic waist: a marker of atherogenic metabolic triad in men? *Circulation* 2000;102:179-84.
7. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415-28.
8. National Cholesterol Education Program. Executive summary of the third report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel-III). *JAMA* 2001;285:2486-97.
9. Alberti KGMM, Zimmet P, Shaw J. For the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome; a new worldwide definition. *Lancet* 2005;366:1059-62.
10. Deedwania PC, Gupta R. East Asians, South Asians, and Asian and Pacific Islander Americans. In: Wong ND, Black HR, Gardin JM. *Preventive cardiology: a practical approach.* 2nd Ed. New York McGraw Hill. 2005;456-72.
11. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2004;111:1448-54.
12. Misra A, Chudhary D, Vikram NK, *et al.* Insulin resistance and clustering of atherogenic risk factors in women belonging to low socioeconomic strata in urban slums of north India. *Diab Res Clin Pract* 2002;56:73-75.
13. Deepa R, Shantirani CS, Premalatha G, Sastry NG, Mohan V. Prevalence of insulin resistance syndrome n a selected south Indian population. *Ind J Med Res* 2002;115:118-27.
14. Ramachandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay V. Metabolic syndrome in urban Asian Indians adults: a population study using modiied ATP III criteria. *Diab Res Clin Pract* 2003;60:199-204.
15. Gupta R, Deedwania PC, Gupta A, Rastogi S, Panwar RB, Kothari K. Prevalence of metabolic syndrome in an Indian urban population. *Int J Cardiol* 2004;97:257-61.
16. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutrition* 2004;20:482-91.
17. Grundy SM, Cleeman JI, Daniels SR, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart Lung and Blood Institute

scientific statement. *Circulation* 2005;112:2735-52.
18. Gupta R, Sarna M, Thanvi J, Rastogi P, Kaul V, Gupta VP. High prevalence of multiple coronary risk factors in Punjabi Bhatia community: Jaipur Heart Watch-3. *Indian Heart J* 2004;57:646-52.
19. Gupta R, Deedwania PC. The metabolic syndrome and obesity. In: Mohan V, Rao GHR. Editors. *Diabetes in South Asia* In Press.
20. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med* 2002;346:591-602.
21. Haslam DW, James WPT. Obesity. *Lancet* 2005;366:1197-1209.
22. Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: evaluation of pathological and therapeutic outcomes. *Am Heart J* 2005;149:20-32.
23. Toumilheto J, Lindstrom J, Eriksson JG, *et al.* Prevention of type 2 diabetes mellitus with lifestyle intervention or metformin. *N Engl J Med* 2001;344:1343-50.
24. Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
25. Stern L, Iqbal N. Seshadri P, *et al.* The effects of low carbohydrate versus conventional weight loss diets in severely obese adults: one year follow-u of a randomized trial. *Ann Intern Med* 2004;140:778-85.
26. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction. *JAMA* 2005;293; 43-53.
27. Knowler WC, Hamman RF, Edelstein SL, *et al.* Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes* 2005;54:1150-56.
28. Diabetes Prevention Program Research Group. Role of insulin sensitivity and secretion in the evolution of type 2 diabetes in the Diabetes Prevention Program. *Diabetes* 2005;54:2404-14.
29. Ornish D, Brown SE, Scherwitz LW, *et al.* Can lifestyle changes reverse heart disease? *Lancet* 1990;336:129-33.
30. Patel C, Marmot MG, Terry DJ, *et al.* Trial of relaxation in reducing coronary risk: four year follow-up. *BMJ* 1985;290:2001-07.
31. Manchanda SC, Narang R, Reddy KS, *et al.* Retardation of coronary atherosclerosis with yoga lifestyle intervention. *J Assoc Physicians India* 2000;48:687-94.
32. Damodaran A, Malathi A, Patil N, *et al.* Therapeutic potential of yoga practices in modifying cardiovascular risk profile. *J Assoc Physicians India* 2002;50:633-40.
33. Vijayraghavan K, Deedwania PC. The renin angiotensin system as a therapeutic target to prevent diabetes and its complications. *Cardiol Clin* 2005;23:165-83.
34. Deedwania PC, Fonesca VA. Diabetes, prediabetes, and cardiovascular risk: shifting the paradigm. *Am J Med* 2005;118:939-47.
35. Krejs GJ. Metabolic benefits associated with sibutramine therapy. *Int J Obesity* 2002;26(Suppl 4):S34-S37.
36. Didangelos TP, Thanapoulou AK, Bousboulas SH, *et al.* The orlistat and cardiovascular risk profile in patients with the metabolic syndrome and type 2 diabetes (ORLICARDIA) study. *Curr Med Res Opin* 2004;20:1393-1401.
37. Hseih CJ, Wang PW, Liu RT, *et al.* Orlistat for obesity: benefits beyond weight loss. *Diab Res Clin Pract* 2005;67:78-83.
38. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study or orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155-61.
39. Pagotto U, Pasquali R. Fighting obesity and associated risk factors by antagonizing cannabinoid type 1 receptors. *Lancet* 2005;365:1363-64.
40. Van Gaal LF, Rissanen AM, Scheen AJ, Zigler O, Rossner S, for the RIO-Europe Study Group. Effects of the cannabinoids-1 receptor blocker rimonabant on wight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005;365:1389-97.
41. Despres JP, Golay A, Sjostrom L, Rimonabant in Obesity-Lipids (RIO-Lipids) Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005;353:2121-34.
42. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, for RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. *JAMA* 2006;295:761-75.
43. Kelley DE. Themodynamics, liposuction and obesity. *N Engl J Med* 2004;350:2542-44.
44. Klein S, Fontana L, Young VL, *et al.* Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004;350:2449-557.
45. Sjostrom L, Lindroos AK, Peltonen M, *et al.* Lifestyle, diabetes and cardiovascular riks factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683-93.
46. Wolfe BM, Morton JM. Weighing in on bariatric surgery: procedure use, readmission rates and mortality. JAMA 2005;294; 1960-63.
47. Grundy SM. Small LDL, atheogernic dyslipidemia and the metabolic syndrome. *Circulation* 1997;95:1-4.
48. Foeber JC, Frohlich JJ, Gerest JJ, *et al.* Recommendations for the management and treatment of dyslipidemia. Report of the working group of hypercholesterolemia and other dyslipidemias. *CMAJ* 2000;162:1441-47.
49. Deedwania PC. TNT study and metabolic syndrome. *Circulation* 2005;112(Suppl A).Abstract.
50. Cottrell DA, Marshall BJ, Falko JM. Therapeutic approaches to dyslipidemia in diabetes mellitus and metabolic syndrome. *Curr Opin Cardiol* 2003;18:301-08.
51. Davidson MH, Toth PP. Combination therapy in the management of complex dyslipidemias. *Curr Opin Lipid* 2004;15:423-31.
52. Paucillo P, Borgnino C, Paoletti R, *et al.* Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidemia (FACT study). Atherosclerosis 2000;150:429-36.
53. Han SH, Quon MJ, Koh KK. Beneficial vascular and metabolic effects of peroxisome proliferator activated receptor-alpha activators. *Hypertension* 2005;46:1086-92.
54. The FIELD study investigators. Effects for long-term fenofibrate therapy in cardiovascular events in 9795 people with type 2 diabetes mellitus (The FIELD study): randomized controlled trial. *Lancet* 2005;366:1849-61.
55. Sharma M, Sharma DR, Singh V, *et al.* Evaluation of efficacy and safety of fixed dose lovastatin-niacin combination in hyperlipidemic patients: a multicentric study. *Vasc Health Risk Management* 2006;2:87-93.
56. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *JACC* 2005;46:1225-28.
57. Brousseau ME, Schaefer EJ, Wolfe ML, *et al.* Effects of an inhibitor of cholesterol ester transfer protin on HDL cholesterol. *N Engl J Med* 2004;350:1505-15.
58. Barted PJ, Kastelein JJP. Targeting cholesteryl ester transfer rotein for the prevention and management of cardiovascular disease. *JACC* 2006;47:492-99.
59. Esler MD. Metabolic syndrome and hypertension: what are the outstanding problems? *Dialogues Cardiovasc Med* 2004;9:167-72.
60. Chobanian AV, Bakris GL, Black HR, *et al.* The seventh report of the joint national committee on prevention, detection,

evaluation and treatment of high blood pressure: the JNC-7 report. *JAMA* 2003;289:2560-72.
61. Barnett AH, Bain SC, Bouter P, *et al.* Diabetics exposed to telmisartan and enalapril study group. Angiotensin receptor blockade versus converting enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952-61.
62. Eriksson KF, Lindgrade F. Prevention of type 2 diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* 1991;34:891-98.
63. Eriksson KF, Lindgrade F. No excess of 12-year mortality in men with impaired glucose tolerance who participated in the Malmo preventive trial with diet and exercise. *Diabetologia* 1998;41:1010-16.
64. Pan XR, Li GW, Hu YH, *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537-44.
65. Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. *Diabetes Care* 2005;28:888-94.
66. Chiasson JL, Josse RG, Gomis R, *et al.* Acarbose for prevention of type 2 diabetes mellitus: STOP-NIDDM randomized trial. *Lancet* 2002;359:2072-77.
67. Buchanan TA, Xiang AH, Peters RK, *et al.* Preservation of pancreatic –cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high risk Hispanic women. *Diabetes* 2002;51:2796-803.
68. Rajagopalan R, Iyer S, Khan M. Effect of pioglitazone on metabolic syndrome risk factors: results of double blind, multi-center, randomized clinical trials. *Curr Med Res Opin* 2005;21:163-72.
69. Dormandy JA, Charbonnel B, Eckland DJA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 2005;366:1279-89.
70. Etgen GJ, Oldham BA, Johnson WT, *et al.* A tailored therapy for the metabolic syndrome: the dual PPAR alpha/gamma agonist LY463608 ameliorates insulin resistance and diabetic hyperglycemia wile improving cardiovascular risk factors in preclinical models. *Diabetes* 2002;51:1083-87.
71. Gerstein H. The ORIGIN study. At: www.cmeondiabetes.com/pub/the.origin.study.php. Accessed 16 March 2006.
72. Patrono C, Garcia-Rodriguez LA, Landolfi R, Baigent C. Low dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;353:2373-83.
73. Wald N, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1149-55.
74. Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischemic heart disease: nested case-control analysis. *BMJ* 2005;330:1059-63.
75. Gupta R, Prakash H, Gupta RR. Economic issues in coronary heart disease prevention in India. *J Hum Hypertens* 2005;19:655-57.
76. Combination Pharmacotherapy and Public Health Research Working Group. Combination pharmacotherapy for cardiovascular disease. *Ann Intern Med* 2005;1443:593-99.
77. Gupta R. Burden of coronary heart disease in India. *Ind Heart J* 2005;57:632-38.
78. Reddy KS, Shah B, Varghese C, Ramadoss A. Responding to the threat of chronic diseases in India. *Lancet* 2005;336:1744-49.
79. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *JACC* 2006;47:1093-1100.

**SADHU VASWANI MISSION'S MEDICAL COMPLEX**
**INLAKS & BUDHRANI HOSPITAL**
**M.N. BUDHRANI CANCER INSTITUTE**

**REQUIRES**

1. **MEDICAL ONCOLOGIST - FULL-TIME :**
Qualification : D.M/DNB - Medical Oncology.
Experience in Bone-marrow transplant desirable.

2. **NEPHROLOGY - CONSULTANT- FULL-TIME :**
Qualification : DM / DNB - Nephrology.
Experience : DNB with 4 years experience. Fresh DM Candidates Can apply.

Candidates to apply along with complete Bio-Data to the **General Manager** at the address given below.

7-9, Koregaon Park, Pune - 411 001.
Tel No. 66099711 Fax No.66099703 Email: inlakspune@vsnl.com