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Insight HEART

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SQUARE PHARMACEUTICALS LTD. BANGLADESH

Cardiovascular Risk Factors: Distribution and Prevalence in a Rural Population of Bangladesh

Coronary heart disease has been emerging as an important public health problem in Bangladesh. Major risk factors for coronary heart disease in most populations include a 'rich' diet, above-optimal levels of total cholesterol and blood pressure, and cigarette smoking. Studies on immigrants from South Asia, including Bangladesh, have identified diabetes mellitus and abdominal obesity as important factors for coronary heart disease. Strategies for preventing premature coronary heart disease include measures to control these risk factors directed towards the population as a whole and individual subjects at high risk.

To plan both the 'population' and 'high-risk' strategies for prevention, the prevalence of major risk factors for coronary heart disease in men and women must be known. Unfortunately, little is known about the distribution of these risk factors in Bangladesh. A few studies have reported the prevalence of individual risk factors such as hypertension, smoking and diabetes mellitus. Cholesterol and obesity have not been addressed, and a comprehensive description of all these factors in a single sample is not available. Zaman M.M. and other fellow researchers tried to describe the distribution and prevalence of these major risk factors in a rural population of Bangladesh.

Non-biochemical variables were examined in 238 men and 272 women aged 18 years or more. Avarage age in men was 38.1 years in women wasd 36.0. Fasting blood glucose and total cholesterol concentrations were determined in a sub-sample of 106 men and 135 women.

Men and women had a similar

- body mass index (20.4 $\pm$ 3.1 vs 20.8 $\pm$ 3.4 kg/m^2),
- waist circumference (72.8 $\pm$ 7.6 vs 71.4 $\pm$ 8.7cm) ,
- systolic blood pressure (118.4 $\pm$ 13.7 vs 119.5 $\pm$ 17.7mmHg),
- diastolic blood pressure (75.9 $\pm$ 9.9 vs 74.6 $\pm$ 11.5mmHg),
- total cholesterol (155.7 $\pm$ 36.0 vs 162.0 $\pm$ 35.2mg/dl) and
- blood glucose level (89.0 $\pm$ 14.9 vs 86.2 $\pm$ 9.6mg/ dl).

After categorization of these variables, the prevalence of

- thinness (body mass index <18.5; 30.0 vs 30.3%) ,
- obesity (body mass index $\geq$ 30; 0.8% vs 1.1%),
- hypertension (systolic blood pressure $\geq$140 and/or diastolic blood pressure $\geq$ 90 or medication; 9.8 vs 15.6%),
- hypercholesterolemia (total cholesterol $\geq$ 240; 2.8 vs 3.0%) and
- diabetes mellitus (blood glucose $\geq$ 126; 2.9 vs 0.7%).

These prevalences are remained similar between the sexes. However, central obesity (waist circumference $\geq$ 94cm in men and $\geq$ 80cm in women) was less frequent in men. Overall, tobacco consumption and smoking were more frequent in men, but chewing tobacco consumption was similar.

Source: Journal of Cardiovascular Risk 2001, 8:103-108

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Metabolic Syndrome And Cardiovascular Disease

Introduction:

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin. Over the past two decades, a striking increase in the number of people with the metabolic syndrome worldwide has taken place. This increase is associated with the global epidemic of obesity and diabetes. With the elevated risk not only of diabetes but also of cardiovascular disease from the metabolic syndrome, there is urgent need for strategies to prevent the emerging global epidemic.

Definition:

WHO and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definitions are given in table 1.

Table 1: Definition of metabolic syndrome

WHO, 1999	ATP III, 2001
Diabetes or impaired fasting glycaemia or impaired glucose tolerance or insulin resistance (hyperinsulinaemic, euglycaemic clamp-glucose uptake in lowest 25%)	
Plus 2 or more of the following	3 or more of the following
Obesity: BMI >30 or waist-to-hip ratio >0·9 (male) or >0·85 (female)	Central obesity: waist circumference >102 cm (male), >88 cm (female)
Dyslipidaemia: triglycerides ≥150 mg/dl or HDL cholesterol < 35 (male) or < 39 (female) mg/dl	Hypertriglyceridaemia: triglycerides ≥150 mg/dl Low HDL cholesterol: < 40 mg/dl (male), < 50 mg/dl (female)
Hypertension: blood pressure ≥140/90 mm Hg	Hypertension: blood pressure ≥130/85 mm Hg or medication
Microalbuminuria: albumin excretion >20 µg/min	Fasting plasma glucose ≥ 110 mg/dl

In retrospect, it is apparent that the WHO definition was better suited as a research tool whereas the NCEP:ATP III definition was more useful for clinical practice. Clinicians prefer simple tools with which to assess patients and improve their management, and it is generally agreed that the NCEP:ATP-III definition is simpler for practice. It requires only a fasting assessment of blood glucose, whereas the WHO definition can require an oral glucose tolerance test. Furthermore, because an accurate assessment of insulin resistance requires a more complicated test (eg, the hyperinsulinaemic euglycaemic clamp technique), its application in an epidemiological or clinical setting is impractical.

NCEP ATP III criteria, applied to an Asian population, will underestimate the population at risk. With a lower waist circumference cutoff , 80 cm in women and 90 cm in men, the prevalence of the metabolic syndrome rises from 12.2 to 17.9% in Asian population. The International Diabetes Federation (IDF) felt, there was a strong need for one practical definition that would be useful in any country for the identification of people at high risk of CVD, but also diabetes. Their recommendations are now available and

Table 2: International Diabetes Federation: metabolic syndrome definition

Central obesity
Waist circumference*- ethnicity specific (see table 3)
Plus any two:
Raised triglycerides
>150 mg/dL (1·7 mmol/L)
Specific treatment for this lipid abnormality
Reduced HDL-cholesterol
<40 mg/dL (1·03 mmol/L) in men
<50 mg/dL (1·29 mmol/L) in women
Specific treatment for this lipid abnormality
Raised blood pressure
Systolic ≥130 mm Hg
Diastolic ≥ 85 mm Hg
Treatment of previously diagnosed hypertension
Raised fasting plasma glucose
Fasting plasma glucose ≥ 100 mg/dL (5·6 mmol/L)
Previously diagnosed type 2 diabetes
If above 5·6 mmol/L or 100 mg/dL, oral glucose tolerance test is strongly recommended,but is not necessary to define presence of syndrome

*If body-mass index is over 30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.

are given in table 2 and 3. Central obesity, as assessed by waist circumference, was agreed as essential (table 2), because of the strength of the evidence linking waist circumference with cardiovascular disease and the other metabolic syndrome components, and the likelihood that central obesity is an early step in the aetiological cascade leading to full metabolic syndrome.

Prevalence

Comparisons of published prevalence for different populations are difficult despite attempts to reach agreement on the definition of the metabolic syndrome. Figure 1 presents prevalance from various countries with NCEP:ATP-III criteria rather than the WHO's. There is wide variation in prevalence in both sexes. In those

Table 3 : Ethnic-specific values for waist circumference

Ethnic group	Waist circumference (as measure of central obesity)
Europids	
Men	≥ 94 cm
Women	≥ 80 cm
South Asian	
Men	≥ 94 cm
Women	≥ 80 cm
Chinese	
Men	≥ 94 cm
Women	≥ 80 cm
Japanese	
Men	≥ 85 cm
Women	≥ 90 cm
Ethnic south & central Americans	Use south Asian data
Sub-Saharan Africans	Use European data
Eastern Mediterranean Arab	Use European data

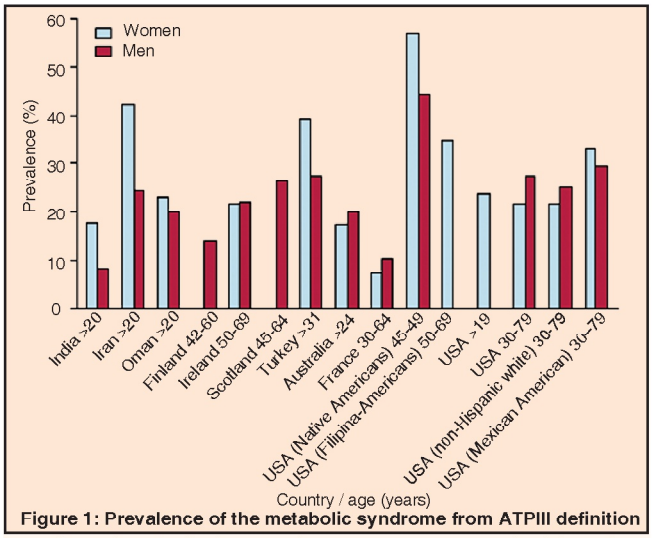

Figure 1: Prevalence of the metabolic syndrome from ATPIII definition

studies that include people 20–25 years and older, the prevalence varies in urban populations from 8% (India) to 24% (USA) in men, and from 7% (France) to 43% (Iran) in women. The prevalence of the metabolic syndrome is highly age-dependent. This pattern is clear in Iran where the prevalence is less than 10% for both men and women in the 20–29 year agegroup, rising to 38% and 67%, respectively, in the 60–69 year age-group.

Relation to predictability of diabetes and cardiovascular disease

The metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease. Several studies have indicated that the metabolic syndrome predicts future diabetes. All metabolic syndrome definitions significantly predicted DM, with odds ratios ranging from 3.4 to 5.4. In the DECODE study involving European men and women, non-diabetic people with the metabolic syndrome had an increased risk of death from all causes as well as from cardiovascular disease.).In MRFIT study, Comparing men with metabolic syndrome to men without, adjusted hazard ratios (HRs) for 18-year total mortality -1.21 (95% CI 1.13 - 1.29), CVD mortality - 1.49 (1.35 - 1.64), coronary heart disease mortality - 1.51 (1.34 - 1.70).

Mechanisms underlying the metabolic syndrome

The cause of the syndrome remains obscure. Reaven proposed that insulin resistance played a causative role, but this remains uncertain. Lemieux et al suggested visceral obesity and the hypertriglyceridaemic waist phenotype as a central component, but this too has been contested. Leptin resistance and Neurotrophic hypothesis are other posible machanisms. Several different factors are probably involved, many related to changes in lifestyle.

Insulin resistance:

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance. Insulin resistance has traditionally been defined with a glucocentric view,i.e. when a defect in insulin action results in fasting hyperinsulinaemia to maintain euglycaemia. A major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. Upon reaching insulin sensitive tissues, excessive fatty acids create insulin resistance by the added substrate availability and by modifying downstream signalling (Figure 2).

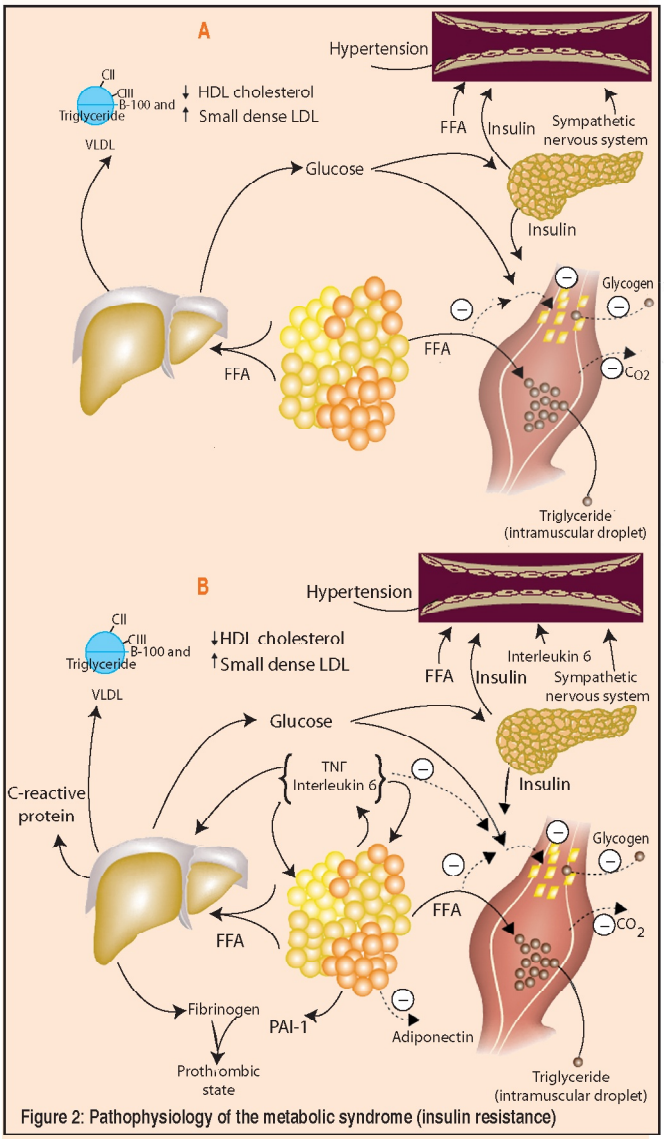

Figure 2: Pathophysiology of the metabolic syndrome (insulin resistance)

Obesity and increased waist circumference:

Mechanistically, a distinction between a large waist due to increases in subcutaneous adipose tissue versus visceral fat is debated.The clinical diagnosis of the metabolic syndrome does not distinguish between increases in subcutaneous and visceral fat. The relative predominance of visceral rather than subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians in contrast to African-American men in whom subcutaneous fat predominates. There is evidence that the elevated

postprandial free fatty acid release in upper body obese women originates from the non-splanchnic upper body fat, and not from the visceral depot. These results suggest that visceral fat might be a marker for, but not the source of, excess postprandial free fatty acids in obesity.

Dyslipidaemia

In the setting of insulin resistance, increased flux of free fatty acids to the liver increases hepatic triglyceride synthesis and increased production of apo B-containing triglyceride-rich very low-density lipoproteins (VLDL) occurs. The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism which results in an increased clearance of HDL from the circulation. In addition to HDL, the composition of LDL is also modified in a similar way. In fact, with fasting serum triglycerides 2·0 mmol/L, almost all patients have a predominance of small dense LDL. This change in LDL composition is attributable to relative depletion of unesterified cholesterol, esterified cholesterol, and phospholipid with either no change or an increase in LDL triglyceride. Small dense LDL might be more atherogenic than buoyant LDL because (1) it is more toxic to the endothelium; (2) it is more able to transit through the endothelial basement membrane; (3) it adheres well to glycosaminoglycans; (4) it has increased susceptibility to oxidation; and/or (5) it is more selectively bound to scavenger receptors on monocyte-derived macrophages; however, this contention is not entirely accepted. In some studies, this alteration in LDL composition is an independent risk factor for cardiovascular disease. However, more often this association is not independent, but related to the concomitant changes in other lipoproteins and other risk factors.

Hypertension

The relation between insulin resistance and hypertension is well established, and relates to several different mechanisms. In the setting of insulin resistance, the vasodilatory effect of insulin can be lost, but the renal effect on sodium reabsorption preserved. Fatty acids themselves can mediate relative vasoconstriction. Insulin also increases the activity of the sympathetic nervous system, an effect that might also be preserved in the setting of the insulin resistance.

Proinflammatory cytokines

The association of the metabolic syndrome with inflammation is well documented. The increases in proinflammatory cytokines including interleukin 6, resistin, tumour necrosis factor (TNF) and C-reactive protein reflect overproduction by the expanded adipose tissue mass (figure 2B).

Beyond insulin resistance

An alternative concept suggested by Unger to explain the metabolic syndrome is leptin resistance. In general, conditions in which leptin deficiency or resistance are present are associated with triglyceride accumulation in non-adipose organs (eg, liver, muscle, and the islets).

Management of metabolic syndrome

Goals of Clinical Management

The primary goal of clinical management in individuals with the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. Even in people with the metabolic syndrome, first-line therapy is directed toward the major risk factors: LDL-C above goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. For individuals with established diabetes, risk factor management must be intensified to diminish their higher risk for Atherosclerotic Cardiovascular Disease (ASCVD).

Component of Clinical Management

Lifestyle modification and drug therapy are the two components of clinical management. The prime emphasis in management of the metabolic syndrome per se is to mitigate the modifiable, underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. Effective lifestyle change will reduce all of the metabolic risk factors. Then, if absolute risk is high enough, consideration can be given to incorporating drug therapy to the regimen. The priority of drug therapy is elevations of LDL-C, blood pressure, and glucose; current guidelines for their management should be followed. Moreover, efforts should be made to bring about smoking cessation in any cigarette smokers. Table 4 summarizes the current goals and recommendations for management of each of the risk factors of the metabolic syndrome. These recommendations are derived in large part from existing NHLBI, AHA, and ADA guidelines for management of specific risk factors.

Risk Assessment

A series of studies have found that many middle-aged people with the metabolic syndrome are at increased absolute risk for ASCVD in the near future (eg, 10-year risk). Framingham investigators find little or no increase in predictive power for CHD by adding abdominal obesity, triglycerides, or fasting glucose to their 10-year risk algorithm. Individuals with metabolic syndrome need to be categorized according to absolute 10-year risk according to ATP III and its update and are catagorized to four groups.

1. High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes transient ischemic attack or stroke of carotid origin or 50% carotid stenosis.

   Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease *plus* any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and

TABLE 4. Therapeutic Goals and Recommendations for Clinical Management of Metabolic Syndrome

Therapeutic Target and Goals of Therapy	Therapeutic Recommendations
Lifestyle risk factors	Long-term prevention of CVD and prevention (or treatment) of type 2 diabetes mellitus
Abdominal obesity Reduce body weight by 7% to 10% during year 1 of therapy. Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI 25 kg/m2)	Consistently encourage weight maintenance/reduction through appropriate balance of physical activity, caloric intake, and formal behavior-modification programs when indicated to maintain/achieve waist circumference of < 40 inches in men and < 35 inches in women. Aim initially at slow reduction of 7% to 10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably 60 min) 5 d/wk, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or an exercise test, to guide prescription. Encourage 30 to 60 min of moderate-intensity aerobic activity: brisk walking, preferably daily, supplemented by increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, housework). Longer exercise times can be achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet Reduced intake of saturated fat, trans fat, cholesterol	Recommendations: saturated fat < 7% of total calories; reduce trans fat; dietary cholesterol < 200 mg/dL; total fat 25% to 35% of total calories. Most dietary fat should be unsaturated; simple sugars should be limited.
Metabolic risk factors	Shorter-term prevention of CVD or treatment of type 2 diabetes mellitus
Atherogenic dyslipidemia Primary target: elevated LDL-C (see Table 5 for details) Secondary target: elevated non-HDL-C High-risk patients : <130 mg/dL (3.4 mmol/L) (optional: 100 mg/dL [2.6 mmol/L] for very high-risk patients) Moderately high-risk patients : <160 mg/dL (4.1 mmol/L) Therapeutic option: <130 mg/dL (3.4 mmol/L) Moderate-risk patients : <160 mg/dL (4.1 mmol/L) Lower-risk patients : 190 mg/dL (4.9 mmol/L) Tertiary target: reduced HDL-C No specific goal: Raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia	Elevated LDL-C (see Table 5 for details) Elevated non-HDL-C Follow strategy outlined in Table 5 to achieve goal for LDL-C First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy Give preference to adding fibrate or nicotinic acid in high-risk patients Give preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients All patients: If TG is ≥500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy) Reduced HDL-C Maximize lifestyle therapies: weight reduction and increased physical activity Consider adding fibrate or nicotinic acid after LDL-C-lowering drug therapy as outlined for elevated non-HDL-C
Elevated BP Reduce BP to at least achieve BP of <140/90 mm Hg (or <130/80 mm Hg if diabetes present). Reduce BP further to extent possible through lifestyle changes.	For BP ≥120/80 mm Hg: Initiate or maintain lifestyle modification in all patients with metabolic syndrome: weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products For BP ≥140/90 mm Hg (or ≥130/80 mm Hg for individuals with chronic kidney disease or diabetes): As tolerated, add BP medication as needed to achieve goal BP
Elevated glucose For IFG, delay progression to type 2 diabetes mellitus. For diabetes, hemoglobin A_{1C} <7.0%	For IFG, encourage weight reduction and increased physical activity. For type 2 diabetes mellitus, lifestyle therapy, and pharmacotherapy, if necessary, should be used to achieve near-normal HbA1C (<7%). Modify other risk factors and behaviors (eg, abdominal obesity, physical inactivity, elevated BP, lipid abnormalities).
Prothrombotic state Reduce thrombotic and fibrinolytic risk factors	High-risk patients: Initiate and continue low-dose aspirin therapy; in patients with ASCVD, consider clopidogrel if aspirin is contraindicated. Moderately high-risk patients: Consider low-dose aspirin prophylaxis
Proinflammatory state	Recommendations: no specific therapies beyond lifestyle therapies

multiple risk factors of metabolic syndrome.

2. Moderately high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%.

3. Moderate-risk patients are those with 2 major risk factors and 10-year risk <10%.

4. Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk <10%.

Management of Underlying Risk Factors

Abdominal Obesity

Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome. Goals and recommendations are given in the table 4. This will require decreasing caloric intake by 500 to 1000 calories per day. Currently available weight-loss drugs possess limited utility in the management of obesity. Nevertheless, in some patients they may be helpful. Bariatric surgery is being used increasingly in the United States for severe obesity. Individuals at high risk for the complications of obesity may benefit.

Physical Inactivity

Increasing physical activity assists in weight reduction; it also has beneficial effects on metabolic risk factors; and importantly, it reduces overall ASCVD risk. Current recommendations for the public call for accumulation of 30 minutes of moderate-intensity exercise, such as brisk walking, on most, and preferably all, days of the week; even more exercise adds more benefit. Thus, going beyond current recommendations will be particularly beneficial for people with the metabolic syndrome. Sixty minutes or more of continuous or intermittent aerobic activity, preferably done every day, will promote weight loss or weight-loss maintenance. Preference is given to 60 minutes of moderate intensity brisk walking to be supplemented by other activities. The latter include multiple short (10- to 15 minute) bouts of activity (walking breaks at work, gardening, or household work), using simple exercise equipment (eg, treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance

training; avoiding common sedentary activities in leisure time (television watching and computer games) is also advised. Self-monitoring of physical activity can help to achieve adherence to an activity program.

Current AHA guidelines call for clinical assessment of risk for future ASCVD events before initiating a new exercise regimen. This includes a detailed history of physical activity. For high-risk patients (eg, those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under medical supervision. AHA guidelines further recommend exercise testing before vigorous exercise in selected patients with cardiovascular disease and other patients with symptoms or those at high risk.

Atherogenic and Diabetogenic Diets

Goals and recommendations are given in table 4.
In addition, there should be ample intakes of fruits, vegetables, and whole grains; fish intake should be encouraged. Very high carbohydrate intakes can exacerbate the dyslipidemia of the metabolic syndrome. ATP III recommended that for individuals entering cholesterol management the diet should contain 25% to 35% of calories as total fat. If the fat content exceeds 35%, it is difficult to sustain the low intakes of saturated fat required to maintain a low LDL-C. On the other hand, if the fat content falls below 25%, triglycerides can rise and HDL-C levels can decline; thus, very-low-fat diets may exacerbate atherogenic dyslipidemia. To avoid any worsening of atherogenic dyslipidemia in patients with the metabolic syndrome, some investigators favor fat intakes in the range of 30% to 35%; others, however, are concerned about possible weight gain resulting from long-term ingestion of higher fat intakes and thus prefer intakes in the range of 25% to 30%.

Effective weight loss requires a combination of caloric restriction, physical activity, and motivation; effective lifelong maintenance of weight loss essentially requires a balance between caloric intake and physical activity.

Management of Metabolic Risk Factors

Beyond lifestyle therapies directed toward underlying risk factors, attention must be given to the metabolic risk factors. If ASCVD or diabetes is present, or if the 10-year risk as determined by Framingham risk factors is relatively high, then drug therapies for risk factors may be required as defined by current guidelines. Recommended principles of management for each of the metabolic risk factors are also considered in Table 4.

Atherogenic Dyslipidemia

As noted before, this condition consists of abnormal levels of triglycerides and apoB, small LDL particles, and low HDL-C. According to ATP III, atherogenic dyslipidemia can become a target for lipid-lowering therapy after the goal for LDL-C has been attained. In other words, as long as LDL-C remains above goal level, LDL-C is the primary target of therapy even in the metabolic syndrome. Other lipid risk factors are secondary. The LDL-C goals depend on estimates of absolute risk. Table 5 reviews LDL-C goals that are consistent with recommendations of ATP III and its recent update. In patients with atherogenic dyslipidemia in whom serum triglyceride levels are ≥200 mg/dL, non-HDL-C becomes the next target of treatment after the LDL-C goal is reached (Table 4). A related and potential secondary target is an elevated total apoB; this measure denotes the number of atherogenic lipoproteins in circulation. Some investigators hold that total apoB is superior to non-HDL-C as a target of lipid-lowering therapy. ATP III nonetheless identified non-HDL-C rather than total apoB as a secondary target (after LDL-C) because accurate measurement of non-HDL-C is more readily available in clinical practice. Goals for non-HDL-C parallel those for LDL-C except that the former are 30 mg/dL higher (Table 4).

When triglycerides are ≥500 mg/dL, triglyceride-lowering drugs should be considered to prevent the development of acute pancreatitis. To achieve non-HDL-C goals at triglycerides 500 mg/dL, triglyceride-lowering drugs may be useful in combination with LDL-lowering therapy. Beyond lowering of non-HDL-C, a tertiary aim in patients with atherogenic dyslipidemia is to raise HDL-C when it is reduced. No specific goal of therapy is recommended for low HDL-C, but HDL-C should be raised to the extent possible after attaining goals for LDL-C and non-HDL-C.

If non-HDL-C remains elevated after the LDL-C goal is reached (Table 5), at least 2 therapeutic options are available. First, intensification of LDL lowering often also reduces non-HDL-C. For example, statins lower both LDL-C and non-HDL-C by a similar percentage; moreover, statins reduce risk for ASCVD events in patients with the metabolic syndrome. Second, a triglyceride-lowering drug can be added to LDL-lowering therapy. Both fibrates and nicotinic acid reduce non-HDL-C and reportedly decrease

TABLE 5. Elevated LDL-C: Primary Target of Lipid-Lowering Therapy in People at Risk for ASCVD

Goals of Therapy	Therapeutic Recommendations
High-risk patients: 100 mg/dL (2.6 mmol/L) (for very high-risk patients in this category, optional goal < 70 mg/dL)	High-risk patients: lifestyle therapies† plus LDL-C-lowering drug to achieve recommended goal If baseline LDL-C ≥100 mg/dL, initiate LDL-lowering drug therapy If on-treatment LDL-C ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination) If baseline LDL-C <100 mg/dL, initiate LDL-lowering therapy based on clinical judgment (ie, assessment that patient is at very high risk)
Moderately high-risk patients:<130 mg/dL (3.4 mmol/L) (for higher-risk patients in this category, optional goal is <100 mg/dL (2.6 mmol/L)	Moderately high-risk patients: lifestyle therapies ± LDL-lowering drug if necessary to achieve recommended goal when LDL-C ≥130 mg/dL (3.4 mmol/L) after lifestyle therapies If baseline LDL-C is 100 to 129 mg/dL, LDL-lowering therapy can be introduced if patient's risk is assessed to be in upper ranges of this risk category
Moderate-risk patients: 130 mg/dL (3.4 mmol/L)	Moderate risk patients: lifestyle therapies ± LDL-C lowering drug if necessary to achieve recommended goal when LDL-C >160 mg/dL (4.1 mmol/L) after lifestyle therapies
Lower-risk patients : 160 mg/dL (4.9 mmol/L)	Lower-risk patients: lifestyle therapies ± LDL-C lowering drug if necessary to achieve recommended goal when LDL-C ≥190 mg/dL after lifestyle therapies (for LDL-C 160 to 189 mg/dL, LDL-lowering drug is optional)

risk for ASCVD in patients with the metabolic syndrome/type 2 diabetes mellitus. For this reason, combining a fibrate or nicotinic acid with LDL-C-lowering treatment becomes an option. Both fibrates and nicotinic acid raise HDL-C as well as reduce triglycerides and small LDL particles. If a statin is being used for LDL-C lowering, fenofibrate seems preferable to gemfibrozil because risk for severe myopathy appears to be lower for fenofibrate in combination with statins. One recent report, however, failed to find a difference in myopathy risk between gemfibrozil and fenofibrate when either was used in combination with statins (other than cerivastatin, which is no longer available). Patients with IFG, IGT, or diabetes who are treated with nicotinic acid deserve careful monitoring for worsening of hyperglycemia. Lower doses of nicotinic acid lessen this risk. Whether adding a fibrate or nicotinic acid to statin therapy will reduce cardiovascular events more than a statin alone has not been evaluated adequately in randomized clinical trials; consequently the use of this combination probably should be limited largely to high-risk individuals who stand to gain the most from it. If a fibrate or nicotinic acid is used with a statin, higher doses of the statin generally should be avoided to minimize risks for myopathy or hepatic effects.

Elevated Blood Pressure

Goals and recommendations are given in table 4. When overt hypertension is present without diabetes or chronic kidney disease, the goal for antihypertensive therapy is a blood pressure of <140/90 mm Hg. In the presence of diabetes or chronic kidney disease, the blood pressure goal is <130/80 mm Hg. Beyond these specific treatment goals, lifestyle changes deserve increased emphasis in people with the metabolic syndrome; the goals here are to reduce blood pressure as much as possible even in the absence of overt hypertension and to obtain other metabolic benefits of lifestyle change. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies: weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits and vegetables and low-fat dairy products, in accord with the Dietary Approaches to Stop Hypertension (DASH) diet. If hypertension cannot be adequately controlled by lifestyle therapies, antihypertensive drugs usually are necessary to prevent long-term adverse effects, eg, myocardial infarction, stroke, and chronic kidney disease. The benefits of therapy extend to patients with type 2 diabetes mellitus whose blood pressure is above goal level, and presumably to hypertensive patients with the metabolic syndrome. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in the metabolic syndrome, especially when either type 2 diabetes mellitus or chronic renal disease is present. Indeed, inhibition of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers (ARBs) may lower risk for diabetes itself. ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors in people who have left ventricular dysfunction. The results of a large clinical trial raised the possibility that use of diuretics in patients with IFG or IGT may increase the likelihood of progression to type 2 diabetes mellitus, although diuretics do in fact lower the risk for cardiovascular events. Most investigators in the hypertension field believe that the potential benefit of low-dose diuretics in combination antihypertensive therapy outweighs their risk.

Elevated Fasting Glucose

Metformin, thiazolidinediones, and acarbose will lower risk for type 2 diabetes mellitus in people with IFG or IGT. Except for a preliminary trial with acarbose, no clinical trial evidence is yet available to document that oral hypoglycemic agents will lessen risk for cardiovascular events. Moreover, neither metformin nor thiazolidinediones are recommended in this statement solely for the purpose of preventing diabetes because their cost-effectiveness and long-term safety have not been documented.

Prothrombotic State

People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. For primary prevention, the only available long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antiplatelet agents. These agents, especially aspirin, are recommended in patients with established ASCVD provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. In metabolic syndrome patients who are at moderately high risk for ASCVD events, aspirin prophylaxis is recommended.

Proinflammatory State

People with the metabolic syndrome frequently have a proinflammatory state as shown by elevated cytokines. CRP levels 3 mg/L can be taken to define such a state in a person without other detectable causes. If CRP is measured, the finding of an elevated level supports the need for lifestyle changes. No drugs that act exclusively through this mechanism are available for reducing cardiovascular risk.

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Insight HEART
Vol: 2 No: 1 ; 2006

Cardiology News

Morning BP Surge Predicts Hypertensive Cardiac Hypertrophy

Morning blood pressure surge is associated with hypertensive cardiac hypertrophy, which is independent of ambulatory blood pressure levels. Cardiovascular events are more likely to occur in the early morning and also show seasonal variations. Blood pressure also has a significant diurnal variation and is influenced by psychological and physical stimuli.

Morning surge in blood pressure is an independent predictor of stroke in elderly hypertensive patients. A positive association between blood pressure reactivity and left ventricular mass index was found. The 30 individuals in the morning blood pressure hyper-reactive group had significantly higher left ventricular mass index than the 90 individuals in the non-reactive group.

Am J Hypertens 2005;18:1528-1533.

Common Genetic Variant Renders Many Asians Resistant to Nitroglycerin

New research indicates that up to 50% of Asians carry a genetic polymorphism that makes sublingual nitroglycerin less effective, or even ineffective, for the treatment of angina. Findings from a recent study showed that for nitroglycerin to work mitochondrial aldehyde dehydrogenase-2 (ALDH2) is required. The enzyme is responsible for forming nitric oxide, the metabolite of nitroglycerin. Many Asians have a suboptimal response to nitroglycerin is because they harbor a gene variant - Glu504Lys - that makes ALDH2 virtually inactive. The study involved 111 Chinese patients taking nitroglycerin for heart disease, of whom 31 were nonresponders to the drug. This genetic factor should be considered when administering nitroglycerin to patients, especially Asians.

J Clin Invest 2006.

Sleep Apnea Prevalent in Systolic Heart Failure

Nearly half of patients with systolic heart failure may have sleep disordered breathing, which in turn may worsen the heart disease if not treated. Sleep apnea is particularly dangerous for patients with heart failure because when patients stop breathing, they don't get enough oxygen to the heart, and there is increased sympathetic activity. As a consequence, sleep apnea and heart failure could become a vicious cycle. Patients with obstructive sleep apnea were significantly heavier and had a higher prevalence of habitual snoring than the other patients. It is important to correctly identify whether a patient has obstructive or central sleep apnea, since treatment is different. For obstructive sleep apnea, continuous positive airway pressure (CPAP) is the treatment of choice, but it is contraindicated in those with central sleep apnea. Potential treatments for central sleep apnea include acetazolamide or theophylline, oxygen therapy or implantation of a pacemaker, although he noted that long-term clinical trials have yet to be completed for the latter two treatments.

Int J Cardiol 2006;106:21-28.

Caffeine Lowers Exercise-Induced Myocardial Flow Reserve

Caffeine decreases exercise-induced myocardial blood flow, resulting in a significant decrease in myocardial flow reserve. And these effects are even more pronounced at high altitudes. Caffeine did not influence total cholesterol, low-density lipoprotein, high-density lipoprotein levels, or resting myocardial blood flow at normoxia. However, at hypoxia, resting myocardial blood flow was significantly increased. Results support that exercise-induced hyperemic flow response may at least in part be antagonized by caffeine, indicating that in people, adenosine seems involved in the regulation of myocardial blood flow at exercise.

J Am Coll Cardiol 2006;47:405-410.

Editorial Note

Dear Doctor
We are happy to present the 4th issue of *"Insight Heart"*. It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on *"Metabolic Syndrome and Cardiovascular Disease"*. We will appreciate your thoughtful comments to enrich the publication.
Thanks and regards.

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