Blunting the Impact of Metabolic Syndrome

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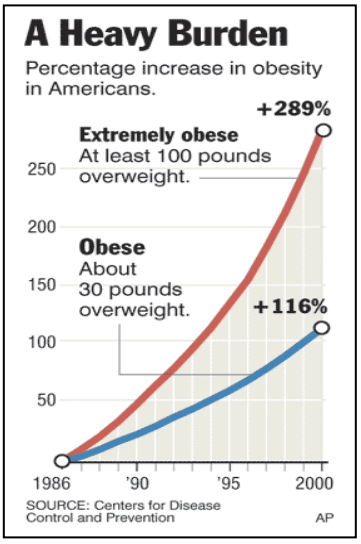
The “double whammy” of the aging of the population and the dangerous increase in inactivity and obesity in younger people threatens to bring about an epidemic of atherothrombotic cardiovascular disease (CVD) greater than previously imagined. This epidemic is linked to a dramatic increase in the prevalence of type II diabetes mellitus (T2DM), which is expected to double within the next 25 years. People with T2DM have a 3-4 times greater risk of developing CVD than those without DM. Metabolic Syndrome (MetS) is a cluster of metabolic abnormalities that often precedes DM.[1] This *Heartbeat* will define MetS and outline strategies to blunt its impact on increasing the risk of developing both DM and CVD.

A Heavy Burden

Obesity is an urgent and growing health problem in the United States. Americans are not just getting fat; they are ballooning to extremely obese proportions at an alarming rate. As overweight and obesity continue to increase dramatically in the U.S., there is a growing incidence of MetS. People with the MetS syndrome are at increased risk for DM and CVD, as well as for increased mortality from CVD and other comorbidities. The prevalence of obesity-related comorbidities emphasizes the need to prevent and treat obesity, rather than just its associated comorbidities.

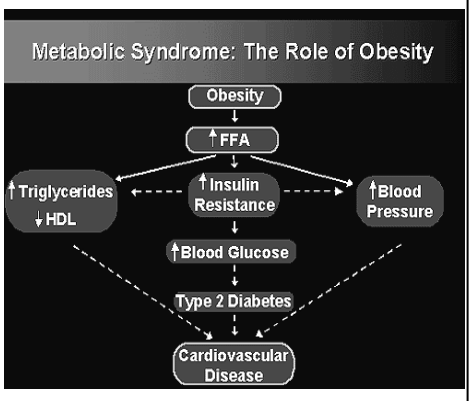


An overweight or obese adult is determined by body mass index (BMI), defined as weight in pounds multiplied by 705, then divided twice by height in inches. A BMI of less than 25 is within normal limits. A BMI of between 25 and 29.9 indicates that an individual is overweight, whereas an obese adult has a BMI of 30 or higher. The risk of death, although modest until a BMI of 30 is reached, increases with an increasing BMI. Obese adults have a 50% to 100% increased risk of premature death compared with adults with a BMI of 20-25. However, even moderate weight excess (10-20 lb for a person of average height), increases the risk of death, particularly among adults aged 30-64 years. The effects of total obesity (BMI) and abdominal obesity (waist or waist/hip measurements) on outcomes are equivalent. Both measures of obesity increase risk of CVD and DM.

Role of Obesity

Many people have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the ***metabolic syndrome***.

Figure 1.



Obesity plays a key role (Figure 1), mediated through an increase in free fatty acids (FFA), resulting in decreased glucose tolerance, abnormal lipid parameters and elevated blood pressure, culminating in diabetes and CVD.

Factors characteristic of the MetS syndrome (also known as cardio-dysmetabolic syndrome, dysmetabolic syndrome X or insulin resistance syndrome) are abdominal obesity, atherogenic dyslipidemia [elevated triglyceride (TG) levels, small low-density lipoprotein (LDL) particles, and low high-density lipoprotein cholesterol (HDL-C) levels], raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states.[2] Diagnostic criteria are outlined in Table 1.

Table I: NCEP Clinical ID of the Metabolic Syndrome*

Risk factor	Defining Level
Abdominal Obesity	Waist Circumference
Men	>40 in
Women	>35 in
Triglycerides (TG)	≥ 150mg/dL
HDL –C	
Men	<40mg/dL
Women	<50mg/dL
Blood pressure	≥130/≥85mmHg
Fasting glucose	≥ 110mg/dL

*Diagnosis is dependent on 3 or more factors

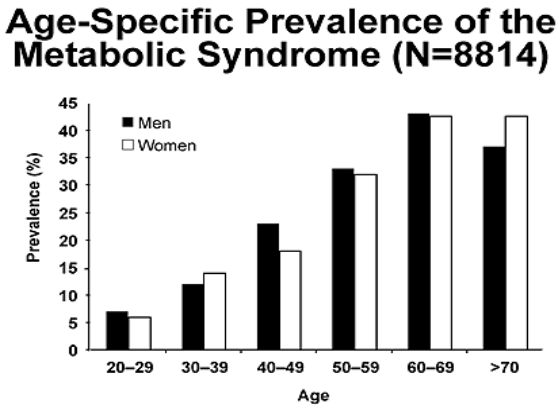
ICD-9-CM Codes:

277.7 MetS (Dysmetabolic Syndrome X)	
Use additional code(s) for associated manifestation(s), such as:	
414.00 - 414.05	Cardiovascular disease
250.01	Diabetes
272.0	Dyslipidemia
278.01	Morbid obesity for surgical treatment

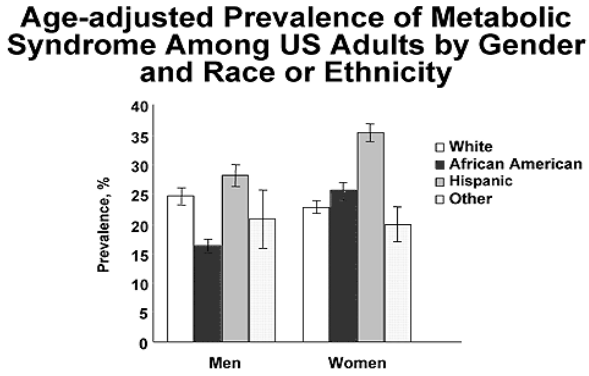
Prevalence

Approximately 47 million Americans—about 1 in 4 adults (23%)—have MetS. This figure includes 10 to 15 million individuals with T2DM.[9] Incidence of MetS in adults is comparable to that of hypertension (24%). As the US population ages, its prevalence will increase steadily among men and women in the older age groups. Prevalence among older segments of the population is already approaching 50% (Figure 2). [3]

Figure 2.

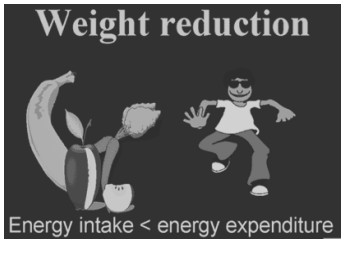


Prevalence in African American women, however, is approximately 57% higher than in African American men, and Hispanic women have a prevalence that is about 26% higher than that seen in their male counterparts (Figure below).[3]



MetS is quite prevalent and reflects the impact of obesity, age, gender, and race. These patients need to be identified and treated, both to lower their risk of CVD and to reduce the risk of progression to T2DM.

The Primacy of Behavior Change



Therapeutic lifestyle change (TLC) is a key therapeutic objective. All components of MetS are positively affected by weight loss and exercise.

Weight loss: Even modest weight reductions, in the range of 5% to 10% of initial body weight, are associated with significant clinical improvement. Successful weight loss requires that more energy be expended than consumed on a daily basis. Studies with formula diets of widely varying composition

have shown that all energy-restricted diets reduce weight and improve glycemic control, lipids and blood pressure. The basis for optimizing CV health for individuals is an overall diet that emphasizes vegetables, fruits, whole grains, fish, and low-fat dairy products, along with regular physical activity. For healthcare practitioners and consulting dietitians, the first step is to convert the patient from a "Western" diet to a "Prudent" diet (Table 3).[4] This will result in a 60% less chance of developing DM.

Table 3. "Western" Diet Vs "Prudent" Diet

Western Diet	Prudent Diet
Red meat	Vegetables
Processed meat	Fruit
French fries	Fish
High-fat dairy products	Poultry
Refined grains—"white carbos"	Whole grains./ carbos in moderation
White rice /potatoes	
Sweets & desserts	

Exercise: There is consensus that virtually all individuals can benefit from regular physical activity—minimum of 30 minutes 5x/week. Although physical activity and exercise are key factors in successful weight reduction programs, the effects are considerably less dramatic than caloric restriction. Regular exercise has also been shown to facilitate maintenance of weight loss because of increased catabolism at 12 weeks. Recent research indicates that men who added exercise to dieting had better discipline and decreased hunger.[5] They also lost more weight than those who dieted without exercise.

An exercise program of moderate physical activity, if undertaken regularly by overweight and obese individuals, can increase maximal oxygen uptake and thus cardiorespiratory fitness—which by itself decreases risk--"survival of the fittest."[6] A minimum of 30 minutes of physical activity of moderate intensity, e.g. brisk walking (>/=3 mph), almost every day is also associated with decreases in blood pressure and lipids. More recent recommendations favor 60 minutes of physical activity daily. TLC is a key determinate for successfully reversing the pathophysiology of MetS through the long-term maintenance of weight loss and fitness—thus preventing or ameliorating CVD and T2DM.

Before starting any physical fitness program, patients > 35 years of age with MetS should be evaluated for fitness and safety (Stress Testing).

Indications for Stress testing in MetS:

Typical or atypical cardiac symptoms
Resting ECG suggestive of ischemia or MI
Occlusive peripheral or carotid arterial disease
Sedentary lifestyle, age ≥35 years, and plans to begin a vigorous exercise program
Two or more of the following risk factors in addition to diabetes
- dyslipidemia
- hypertension
- smoking
- family history of premature coronary heart disease
- microalbuminuria or macroalbuminuria

CV Risk Assessment

It is not clear how aggressive pharmocologic prevention should be in the MetS. The intensity of management of risk factors in the MetS depends on assessment of the patient's global risk for CVD, particularly coronary heart disease (CHD). Patients at higher risk deserve more aggressive risk-reduction therapy. According to ATP III guidelines, risk assessment is best carried out using the Framingham 10yr CHD risk calculator (*attached*). Some clinicians have the mistaken impression that the presence of MetS indicates that a patient has a high-risk status, similar to patients with established CHD or T2DM. But absolute risk in patients with MetS is variable, and some patients are at only moderate or moderately high risk for CHD—age will be a major variable.

Some of the risk factors listed for the MetS are not included in Framingham risk scoring. These include family history, abdominal obesity, physical inactivity, a proinflammatory state [high levels of cardio or high sensitivity C reactive protein (hs-CRP)], high homocysteine or Lp(a), impaired fasting glucose or impaired glucose tolerance, and a prothrombotic state (high levels of fibrinogen). ATP III guidelines do not recommend routine

measurement of these emerging conditional risk factors, but they are listed as optional measures. The hs-CRP, homocysteine and Lp(a) levels should be obtained in patients with characteristics of the MetS and, if found to be abnormal, risk adjusted higher than estimated from Framingham risk scoring. This information can be used as added incentive for patients to comply with diet and exercise programs or possibly consider more aggressive medical therapy. However, this approach is problematic because reliable, quantitative adjustments to risk have not been developed.

Clinical Management of MetS:

TLC

- Reduce weight (enhances LDL-C lowering and reduces all risk factors)
- Exercise (reduces LDL-C and increases HDL-C); beneficial for all risk factors

Treat lipid and non-lipid risk factors
(depending on 10yr CHD risk)

- Hypertension—control BP
- Elevated TG
- Low HDL-C
- Aspirin in CHD and those with > 6% 10yr CHD risk (decreases prothrombotic state)
- glucose > 110mg/dL

Beyond TLC, modification of traditional CVD risk factors has an impressive impact on morbidity and mortality in subjects with diabetes and insulin resistance.

Treatment of BP in MetS (>130/85)

Evidence is accumulating to support the suggestion that drugs which interrupt the renin-angiotensin system (RAS) may be superior for risk reduction and less 'diabetogenic' than some 'older' antihypertensive drugs…especially in MetS. We know that ACE inhibitors are beneficial in T2DM, decreasing progression of both CV and renal disease. Results of HOPE[7], EUROPA[8], ALLHAT[9] and ANBP2[10] have shown reductions in the incidence of DM with ACE inhibitors.

As a drug class, the ARBs have to date played 'second fiddle' to ACE inhibitors, probably because until recently evidence of significant clinical benefit was still awaited. However, this situation is now changing with recognition of their renal-protective properties in T2DM[11] and emerging evidence from the LIFE study[12] and the CHARM trial[13]. Blockade of the angiotensin II receptor resulted in respective 25% and 28% decreases in the incidence of DM.

Control of HBP is imperative as part of the treatment program for MetS. Two or more drugs will probably be needed to obtain proper BP control in MetS and I feel that a diuretic/ACE-inhibitor or diuretic/ARB combination would be the most advantageous—to treat HBP and decrease CV complications—based on recent data.

Treatment of Lipids in MetS

According to guidelines from the Adult Treatment Program III (ATP III) of the National Cholesterol Education Program, LDL cholesterol is the primary target of lipid-lowering therapy. LDL goals should be set according to the absolute risk of patients. Many patients with the MetS will be classified as being at high risk, i.e. they will have established atherosclerotic cardiovascular disease or T2DM, or they will have a 10-year coronary heart disease (10yr CHD) risk >20% by Framingham scoring. Such patients will have an LDL goal <100 mg/dL. Most of the remaining patients with MetS will be at high enough risk to have an LDL goal of <130 mg/dL. If drug therapy is required to achieve the goals of therapy, the statins are the ideal first drug of choice--(proven benefits for both primary and secondary prevention). Statins benefit those with low HDL-C the most[14] and also decrease hs-CRP—a marker of high-risk—commonly occurring in MetS[15].

An unexpected outcome of the West of Scotland Coronary Prevention Study (WOSCOPS)[16], a study of primary prevention with pravastatin, was a 30% reduction with pravastatin in the risk of developing diabetes during the study. Triglyceride-lowering or anti-inflammatory properties of pravastatin were postulated as a possible mechanism. This was not supported in other statin trials.

Based on this information and the Duke Program for Prevention, we look for reasons to bump MetS patients at calculated intermediate risk (10-20% 10yr risk of CHD) to higher risk.[17] (beyond Framingham-attached) If they have any predisposing risk factors, i.e. family history, obesity or physical inactivity or conditional risk factors like elevated hs-CRP, increased homocysteine or lipoprotein (a), we tend to treat them more aggressively with statins.

However, in many patients with MetS, statin therapy alone will not correct abnormalities in triglycerides and low HDL. Especially when the MetS occurs in high-risk patients, consideration can be given to adding a second lipid-lowering drug, e.g., nicotinic acid or fibric acid.

Unfortunately, the combination of statin+fibrate carries increased risk for severe myopathy. Using a water soluble statin (provastatin), instead of the more lipid soluble statins (the others) or just a lower dose statin and fenofibrate (Tricor), which is probably a little safer than gemfibrozil (Lopid), minimizes this risk. The benefit of correcting low HDL-C and high TG (V-HIT) outweighs the risk.[18] Patients should be warned about this risk and should be told to stop both meds if severe muscle aches or weakness occur. Remember myalgias occur frequently but true myopathy is almost always associated with CPKs > 3000u. More frequent monitoring of LFTs and CPK is recommended.

Niacin seems to aggravate blood sugars but again the lipid benefits outweigh this risk and elevated glucose should be treated appropriately.

Treatment of prothrombotic state in MetS

Low-dose aspirin therapy is indicated in all with a 10yr CHD risk > 6%[19] and almost all MetS patients meet these criteria.

Treatment of Elevated Glucose in MetS

TLC and certain medications may lessen the risk of progression from impaired fasting glucose (110-126mg/dL) to frank T2DM (> 126mg/dL). Results of 2 clinical trials completed in the past 2 years are especially important. In the first of these trials, European investigators had patients with impaired fasting glucose follow TLC or their usual lifestyle. After one year, the subjects in the TLC intervention group experienced a 4.2-kg weight loss (versus 0.8 kg in controls) along with minimal improvements in BP, HDL-C and TG, and an 11% rate of new T2DM over 4 years (versus 23% in controls).[20] The 58% (23% versus 11% absolute rates) decreased risk of new T2DM was particularly striking.

The second trial was conducted in the US and enrolled subjects with elevated fasting and post-load plasma glucose levels. The study included 3 arms of therapy: TLC, metformin, and troglitazone. The troglitazone intervention was stopped early because of liver toxicity. In comparisons with placebo users, the persons who followed TLC experienced a 58% lower progression rate to T2DM and the metformin users had a 31% lower development of T2DM.[21] In another glitozone study with troglitazone, there was an associated 55% reduction in DM.[22]

Summary: Tx of MetS

TLC (Diet/exercise)—decreased weight and improved fitness improve and/or prevent all risk factors.

Control BP to <130/85—ACE and diuretic (cheaper) or ARB and diuretic combination—have additional preventative and risk-reduction benefits.

Treat Lipids—Statins—(provastatin is first choice, especially if combination therapy needed—less risk).

Treat low HDL-C and/or high TG—fenofibrate is first choice because of decreased myopathy risk. Niacin increases DM risk and is not as well tolerated—but good success can be obtained with Niacin or niacinSR/statin combination.

Decrease prothrombotic state—ASA 81mg.

Prevent increased glucose and T2DM—our first choice is metformin because of possible associated weight loss. Glitizones are also beneficial.

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Under Patient Education—From Your Physician.
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