METABOLIC SYNDROME
A Resource from the American College of Preventive Medicine

A Clinical Reference
The following Clinical Reference provides evidence to support the Metabolic Syndrome Time Tool.

1. Description/Definitions
2. Diagnostic Criteria
3. Prevalence and Trends
4. Impact on Health and Disease
5. Etiology and Mechanisms
6. Treating the Metabolic Syndrome
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1. DESCRIPTION/DEFINITION

The fattening of the human species and the emergence of the metabolic syndrome and Type 2 diabetes are among the major epidemiologic events of our time. [1]

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III, which provides the current diagnostic standard, describes the metabolic syndrome as a constellation of clinical characteristics associated with an increase in risk of developing type 2 diabetes and atherosclerotic cardiovascular disease. [2]

A general definition: A collection of metabolic abnormalities associated with insulin resistance that predisposes affected individuals to accelerated atherosclerosis and consequently increased risk of cardiovascular events. [3]

The metabolic abnormalities include:
- carbohydrate intolerance,
- a specific pattern of dyslipidemia - increased triglycerides, low HDL cholesterol, small dense LDL cholesterol, increased apolipoprotein B
- hypertension
- endothelial dysfunction
- increased coagulation
- decreased fibrinolysis, and
- microalbuminuria [4]

Central, abdominal, or visceral obesity appears to be a major etiologic factor for the insulin resistance and other factors of the metabolic syndrome. [3]
- It is commonly associated with pre-diabetic hyperinsulinemia, which contributes greatly to the metabolic dysfunction.
- This combination of metabolic abnormalities, especially when occurring together, contributes to endothelial dysfunction, inflammation and an accelerated rate of atherosclerosis. [5]

It is part of the natural course of developing impaired glucose tolerance and Type 2 diabetes -- from insulin resistance to hyperinsulemia to impaired glucose tolerance to hyperglycemia to diabetes. [6,7]
- It is progressive, with borderline risk factors worsening over time.

The metabolic syndrome is thought to be a driver of the modern day epidemics of diabetes and CVD; as such, it has become a major, and growing, public health challenge around the world. [9]
- It has enormous clinical and public health implications by providing a simple way to identify individuals at greatly increased risk of suffering these devastating diseases.

History of the Metabolic Syndrome

The clustering of risk factors that has become the "Metabolic Syndrome" came primarily from the diabetes field. The pathology of Type 2 diabetes and the role of insulin resistance had been studied for years. But the concept of the syndrome was introduced in 1988 by Reaven in the "Banting" Lecture of the ADA Annual Meeting -- "Role of insulin resistance in human disease". He coined the initial name, "Syndrome X". [7]

He described insulin resistance as the dominant underlying risk factor that leads to progressively disrupted metabolism. This eventually led others in the diabetes field to later adopt the name, "Insulin Resistance Syndrome". [10-14]

They largely viewed obesity as an exacerbating factor but without the pathophysiological significance of insulin resistance. More recently, Metabolic Syndrome (or Dysmetabolic Syndrome) has become the more commonly used name, reflecting the broader scope of underlying factors in the development of the syndrome. [15-17]
The Cloud of Controversy
The American Diabetes Association (ADA) and the American Heart Association (AHA) disagree when it comes to the Metabolic Syndrome. [18]
  o The ADA emphasizes the association with diabetes, referring to the syndrome as “pre-diabetes.”
  o They discount its use in CVD risk prediction, claiming that it is merely a combination of risk factors that the AHA already includes without calling it the Metabolic Syndrome.

The AHA is actually more enthusiastic about the syndrome than the ADA. [18]
  o They emphasize its importance in CVD prevention and risk assessment – that the specific combination of disorders places these people at a much higher risk, and deserves the increased attention.

The controversy involves four aspects:
  o The varying definitions,
  o Evidence for and against its use in predicting cardiovascular disease risk,
  o Questions about the underlying pathophysiology, and
  o Whether it changes treatment over simply treating the individual conditions. [19]


Gaining Acceptance
The concept of the Metabolic Syndrome continues to gain acceptance as a condition that mandates treatment as a single entity rather than as individual conditions. [20]
  o An important value of the syndrome is the increasing attention to the important link between metabolic alterations and cardiovascular events.
  o Each risk factor of the syndrome (visceral obesity, atherogenetic dyslipidemia, elevated blood pressure, and dysglycemia) can be dealt with individually, but the optimal therapeutic approach is to focus on reversing its root causes of atherogenic diet, sedentary lifestyle, and overweight or obesity. [21]

The most important function of identifying the syndrome in an individual is the focus it places on lifestyle – the entire syndrome is best treated by adopting a healthy diet and becoming more active. [21]
  o The root causes are too little physical activity combined with an atherogenic diet – it results in weight gain and the metabolic syndrome in genetically susceptible people.

The metabolic syndrome provides an early warning of at risk subjects and emphasizes the need to treat more aggressively by lifestyle modification patients with multiple abnormalities even though the abnormalities might be slight.
  o The syndrome can be easily used in clinical practice and when assessed against the background of the age, sex and smoking habits, provides an evaluation of potential cardiovascular risk. [22]

Lack of Awareness
The Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD), a longitudinal US population-based survey initiated in 2004, showed that less than 15% of respondents had even heard of the metabolic syndrome. [23]
  o The lack of knowledge about metabolic syndrome indicates limited penetration of this concept into public awareness.
2. DIAGNOSTIC CRITERIA

The NCEP-ATP III report included the definition of the metabolic syndrome that is now most widely used:
- Any 3 of the 5 defining criteria:
  - abdominal obesity: waist circumference $\geq 40''$ in men, $\geq 35''$ in women,
  - elevated triglycerides: $\geq 150$ mg/dL or on drug therapy for elevated triglycerides,
  - low HDL cholesterol: $< 40$ mg/dL in men or $< 50$ mg/dL in women or on drug therapy for low HDL,
  - borderline hypertension: $\geq 130/85$ or on drug therapy for elevated blood pressure,
  - fasting hyperglycemia: $\geq 100$ mg/dL or on drug therapy for elevated glucose. [2]

http://circ.ahajournals.org/cgi/content/full/112/17/e285/TBL1

- Lower waist circumference cut points (i.e., $\geq 35$ inches in men and $\geq 31$ inches in women) appear to be appropriate for Asian Americans. [2]

The defining criteria for the syndrome has been a source of controversy and the subject of many symposia around the world. The first published definition was from the World Health Organization (WHO) in 1998, along with its related European Group for the Study of Insulin Resistance (EGIR) guidelines. [24,25]

In 2001, at the urging of the American Association of Clinical Endocrinologists (AACE), a new ICD-9 code (277.7) for the "dysmetabolic syndrome" was approved. [26]
- ICD-9 CODE 277.7 Dysmetabolic syndrome X
- Use additional codes for associated manifestation, such as:
  - cardiovascular disease (414.00-414.07)
  - obesity (278.00-278.01)

In the same year, the National Cholesterol Education Project Adult Treatment Panel (NCEP-ATP III) published its expert panel report and guidelines, using the name "Metabolic Syndrome" because it seemed to better describe the constellation of risk-factors and their underlying pathology. [2,27]

The American College of Endocrinology (ACE) subsequently published a position statement in collaboration with American Association of Clinical Endocrinologists (AACE) on "insulin resistance" (their preferred term), which uses BMI rather than waist circumference to measure central obesity, introduces ethnicity as a risk factor, and emphasizes that diagnosis should be based on clinical judgment informed by the evaluation of risk factors. [28]

The most recent definition of the metabolic syndrome was released by the International Diabetes Federation (IDF) in 2005. [29]
- It is the same as the NCEP definition, except that it requires meeting the waist circumference criteria first, then any two others; this reflects the growing recognition of the key role of central obesity.
- It also uses a slightly lower waist circumference threshold, as well as ethnicity specific thresholds.
- But, requiring abdominal adiposity means missing non-obese individuals who have increased CVD mortality. [30]

The NCEP-ATP III is the simplest criteria and the most suitable for clinical practice. [31]
- The IDF criteria are a little more complex and have not been as well evaluated.

The table below compares the definitions of the NCEP-ATP III and the IDF.
Table. Current Criteria for the Diagnosis of the Metabolic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>NCEP-ATP III</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>Current antihypertensive therapy OR SBP ≥ 130 OR DBP ≥ 85</td>
<td>Current antihypertensive therapy OR BP ≥ 130/85</td>
</tr>
<tr>
<td><strong>Dyslipidemia - Elevated Triglycerides</strong></td>
<td>Plasma triglycerides ≥ 150 mg/dL</td>
<td>Plasma triglycerides ≥ 150 mg/dL or specific treatment for high triglycerides</td>
</tr>
<tr>
<td><strong>Dyslipidemia - Depressed HDL</strong></td>
<td>HDL &lt; 40 mg/dL in men or &lt; 50 mg/dL in women</td>
<td>HDL &lt; 40 mg/dL in men or &lt; 50 mg/dL in women or specific treatment for low HDL</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>Waist circumference ≥ 40 inches in men or ≥ 35 inches in women</td>
<td>Waist circumference &gt; 37 inches in men or &gt; 31.5 inches in women</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>Fasting blood glucose ≥ 100 mg/dL</td>
<td>Fasting glucose ≥ 100 mg/dL OR previously diagnosed type 2 diabetes</td>
</tr>
<tr>
<td><strong>Requirements for diagnosis</strong></td>
<td>Any 3 of the above criteria.</td>
<td>Waist circumference criteria PLUS any 2 of other criteria.</td>
</tr>
</tbody>
</table>

NCEP-ATP III = National Cholesterol Education Project Adult Treatment Panel; IDF = International Diabetes Federation; BP = blood pressure; HDL = high-density lipoprotein; BMI = body mass index; IGT = impaired glucose tolerance


Improving the Diagnostic Capability -- Potential New Criteria

**Insulin Resistance**

Insulin resistance and the resulting compensatory hyperinsulinemia are clearly key pathophysiologic factors. Simple, valid and reliable measurements of each would be very helpful but such measures are not currently available (standardized fasting insulin assays), or practical (insulin resistance tests) in the clinical setting. [32,33]

○ The gold standard for insulin resistance is the euglycemic hyperinsulinemic clamp method, but it is too time consuming and expensive to use for screening.

**Adiponectin**

The recently discovered adipokine, adiponectin, has been shown to reflect insulin resistance (lower level = greater resistance). Data from the Rancho Bernardo Study suggest that measurement of adiponectin levels could eventually become a useful way to test for early risk for the development of the metabolic syndrome.

○ Age-adjusted total adiponectin concentration at baseline was found to be lower in those who eventually developed the metabolic syndrome. [34]

**C-Reactive Protein**

Adding CRP, as a marker of inflammation, to the definition of the Metabolic Syndrome has been shown to improve the prediction of CVD, and may also be predictive of development of the metabolic syndrome. [35]

○ CRP is being used to improve vascular risk prediction in primary and secondary prevention trials across all levels of low-density lipoprotein-cholesterol (LDL-C), all levels of the Framingham Risk Score, and all levels of metabolic syndrome. [36]
Using the Triglyceride/HDL ratio
The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio may be a clinically simple and useful indicator for hyperinsulinemia among nondiabetic adults regardless of race/ethnicity. [37]

Additional lipoprotein testing
The 2008 ADA/ACC consensus statement discusses the use of apolipoprotein B testing as well as LDL particle testing to differentiate MetS dyslipidemia. [See Resources, Consensus Statements]

3. PREVALENCE AND TRENDS

NHANES 1999-2000, using the NCEP definition, showed the prevalence of the metabolic syndrome to be 34.5% overall, 33.7% among men, and 35.4% among women. [38]
  o Using the IDF criteria (lower waist circumference), the prevalence increased to 39.0 % among all participants, 39.9% among men, and 38.1% among women. This primarily reflected an increased prevalence in Mexican-American men (lower waist threshold).
  o The two definitions correctly classified approximately 93% of the participants as having or not having the metabolic syndrome.

As the population ages, so does the prevalence of the Metabolic Syndrome. One analysis shows about 45% of the population over 60 to have the syndrome. [39]
  o Studies suggest that 1 of every 3 people born in the year 2000 will develop diabetes, and if present trends continue, for Latino and African Americans born in 2000, the risk approaches 1 in 2.

And it is being seen at younger and younger ages, in parallel with the rising incidence of obesity. [40]
  o NHANES data show that the prevalence of the metabolic syndrome in 12- to 19-year-olds increased from 9.2% in 1988-1994 to 12.7% in 1999-2000.
  o Even more alarming is the prevalence in overweight adolescents -- 38.6% vs 1.4% in normal-weight adolescents.

There are gender differences in the syndrome as well.
  o Prevalence has been increasing at a steeper rate in women during the last decade; this may be contributing to the increased rate of CVD in postmenopausal women who are more prone to central obesity. [41]

Of the individual components of the syndrome, fasting hyperglycemia is the last to develop, reflecting the natural course of the developmental process:
  o Insulin resistance ⇒ Hyperinsulinemia ⇒ Impaired glucose tolerance ⇒ Fasting hyperglycemia ⇒ Type 2 diabetes [7]

This is reflected in the prevalence of individual components of the MS reported in NHANES III:

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased waist</td>
<td>30%</td>
<td>46%</td>
</tr>
<tr>
<td>Triglycerides &gt; 150</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>Low HDL</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38%</td>
<td>29%</td>
</tr>
<tr>
<td>Fasting glucose &gt; 110</td>
<td>16%</td>
<td>10%</td>
</tr>
</tbody>
</table>


The Mirror Image -- Rising Obesity
In 1980, 13% of men and 17% of women were obese; today 28% of men, 34% of women.
The same trend is seen in children, rates obesity increased from 6% to 15% in 6-11 yr olds and from 5% to 16% in 12-19 yr olds over the same 20 yr period, 1980-2000. [42]

From NHANES III (1988-94) to NHANES 1999-00, the prevalence of overweight increased from 56% to 65% of the population and the prevalence of obesity increased from 23% to 31%. [43]

Nearly 2 out of every 3 are overweight, 1 of 3 obese, a striking statistic that has an enormous impact on the health of the nation.

NHANES data from 1999-2004 shows that over half of people with hypertension are currently obese. [44]

An ominous trend is the rise in abdominal obesity – fat accumulated in the trunk as opposed to the lower body; fat that is closely associated with the metabolic syndrome.

NHANES data shows that the average waist circumference has steadily increased in both men and women over the last 40 years, but especially the last 10 years. [45]

NHANES 2003-4 showed that over half of U.S. adults (42% of men, 61% of women) had abdominal obesity. [46]

<table>
<thead>
<tr>
<th>Waist Circumference (inches)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960-1962</td>
<td>35</td>
<td>30.3</td>
</tr>
<tr>
<td>1988-1994</td>
<td>37.4</td>
<td>35</td>
</tr>
<tr>
<td>2003-2004</td>
<td>39.5</td>
<td>37</td>
</tr>
</tbody>
</table>

4. IMPACT ON HEALTH AND DISEASE

Despite the controversies, there is no question about the impact of this collection of risk factors on health and disease. Many researchers have shown that increased insulin resistance and the metabolic syndrome increase the risk for CVD and the development of type 2 diabetes. [44-53] [47-56]

People with the metabolic syndrome are at essentially twice the risk for cardiovascular disease compared with those without the syndrome. It further raises the risk for type 2 diabetes by about 5-fold. [2,57]

Data from more than 154,000 men and 90,000 women in the NIH-AARP Diet and Health Study showed that, after adjustment for BMI and other covariates, a large waist circumference alone was associated with a 25% increased mortality. Even with a normal BMI, a large waist circumference conveyed a 20% increase in mortality risk. [58]

NHANES data shows that adults with the metabolic syndrome experience poorer health-related quality of life than adults without this syndrome. [59]

CARDIOVASCULAR DISEASE

The Metabolic Syndrome is associated with about a two-fold increase in risk of cardiovascular events, independent of the presence of diabetes mellitus. [60]

The doubling of risk was confirmed in a meta-analysis of 9 primary studies published between 2002 and 2004 that was presented at the ADA annual meeting in 2005; it included more than 50,000 patients with a median follow-up of 5 years. [61]

More importantly, longitudinal studies have confirmed that atherosclerosis develops earlier and at a faster rate in people with the metabolic syndrome than those without the syndrome. [62]

The high risk for CVD that results from the MS generally precedes the diagnosis of diabetes by 10-20 years. [63]

An increased prevalence of early subclinical cardiovascular damage has been observed in several studies when the MS includes hypertension. [64]
Several studies have found an increased prevalence of left ventricular hypertrophy, diastolic dysfunction, early carotid atherosclerosis, impaired aortic distensibility, hypertensive retinopathy and microalbuminuria in hypertensive patients with MS compared to those without it.

May partially explain the association of the MS with a higher cardiovascular and renal risk.

The majority of patients without known diabetes or IGT who have a heart attack do, in fact, have diabetes or impaired glucose tolerance that was undetected prior to the infarction. [65]

Only one third of these heart attack survivors actually had neither diabetes nor glucose intolerance.

Death from cardiovascular disease is significantly increased in patients with the metabolic syndrome at all levels of glucose tolerance. The combination of the Metabolic Syndrome with diabetes is particularly hazardous. [66,67]

- NGT w Metab Syn -- 1.73 times risk of CHD than NGT wo metab syn
- IGT w Metab Syn -- 1.82 times risk of CHD than IGT wo metab syn
- DM w Metab Syn -- 2.23 times risk of CHD than DM wo metab syn
- DM w Metab Syn -- 5 times risk of CHD than NGT wo metab syn

Other studies have confirmed these findings.

- The Botnia study from Finland showed that cardiovascular mortality in people with metabolic syndrome is increased 6-fold compared with people without the syndrome over a 7-year period. [67]
- The Kuopio Ischaemic Heart Disease Risk Factor Study reported the risk of death from heart or vascular disease to be about 3-4 fold higher in patients with the metabolic syndrome. [68]

In women, the Nurses’ Health Study has shown that: [63]

- Those with diabetes when the study began had the highest risk for a CV event during 20-year follow-up – 5 times that of those who remained non-diabetic.
- Those diagnosed with diabetes during the study were 4 times as likely to have an event after the diagnosis.
- And those who eventually developed diabetes and thus likely had the metabolic syndrome, had 3 times the risk of having a CV event before they were diagnosed with diabetes.

The associated risk factors have a continuous, progressive impact on total CV risk, with higher levels and numbers of factors translating into greater risk. [69]

Risk for stroke also increased
Meta-analysis of 13 cohorts with the metabolic syndrome showed that they had a 1.6-fold increased risk of stroke. [70]

Is risk from the Metabolic Syndrome greater than expected from traditional risk factors?
Controversy exists as to whether the metabolic syndrome adds anything to cardiovascular risk prediction beyond the individual risk factors that define it. [71]

Data from the San Antonio Heart Study suggests that it does.

- Excess risk was associated with increasing insulin resistance after adjusting for traditional risk factors -- age, ethnicity, LDL cholesterol, triglyceride, HDL cholesterol, systolic blood pressure, smoking, alcohol consumption, leisure time exercise, and waist circumference. [72]

Nontraditional risk factors
Conventional risk formulas underestimate actual CVD risk in patients with the metabolic syndrome because of the influence of nontraditional risk factors. [73]

- As the syndrome evolves, a number of coexisting metabolic abnormalities contribute additional risk.
- This likely explains the disproportionate increase in CVD risk in people with Type 2 diabetes [74]
An increased prevalence of non-traditional risk factors has been observed in patients with diabetes, IGT, IFG and the metabolic syndrome. [75]

- After adjustments for traditional risk factors, the metabolic syndrome is associated with an increased likelihood of abnormal levels of:
  - low apolipoprotein A1 -- 2.27 times as likely as those without the syndrome,
  - high apolipoprotein-B -- 2.97 times as likely,
  - higher HOMA insulin resistance index -- 5.25 times as likely,
  - chronic kidney disease -- 2.27 times as likely, and
  - elevated markers of inflammation [high white blood cell count (1.55 times), and elevated C-reactive protein (1.46 times)].

There is accumulating evidence of the deleterious impact on several of these nontraditional risk factors when the metabolic syndrome is present.

- Inflammation is one --the inflammatory marker, C reactive protein (CRP), appears to modify risk at all levels of the metabolic syndrome. [76]
- Abdominal obesity increases risk even in the absence of traditional risk factors due to the effects of increased adipokines (reduced adiponectin). [77]
- Diabetes is clearly a major risk factor, but accumulating evidence also suggests that prediabetes (either IGT or impaired fasting glucose) increases risk long before diabetes is diagnosed. [78]

Accumulating evidence suggests that several emerging biomarkers may prove useful in defining prognosis for CVD in patients with the MS.

- CRP is one of these, a marker of chronic mild inflammation -- now commonly used in clinical practice to improve vascular risk prediction across all levels of LDL cholesterol, all levels of the Framingham Risk Score, and all levels of metabolic syndrome. [79]
- Others include markers of:
  - increased oxidant stress (oxidized LDL),
  - thrombophilia (e.g. plasminogen activator inhibitor-1, PAI-1),
  - endothelial dysfunction (e.g. E-selectin), and
  - other lipoprotein abnormalities -- lipoprotein-associated phospholipase A2, myeloperoxidase, lipoprotein (a), isoprostanes, and small, dense LDL. [80]

**Greater impact on women**
The Metabolic risk factors of the syndrome have been suggested to portend a greater CHD risk in women than men, especially postmenopausal women. There are parallel epidemics occurring in postmenopausal women -- cardiovascular disease and the metabolic syndrome. [81]

The Nurses’ Health Study has followed almost 120,000 women for over 20 years.

- Women who subsequently developed diabetes, and therefore were most likely to have the metabolic syndrome, had almost 3 times the risk of having an event before they were diagnosed with diabetes.
- Women were almost 4 times as likely to have an event after the diagnosis of diabetes, and women who entered the study with pre-existing diabetes were the most likely to have an event, with 5 times the relative risk. [63]

**RISK FOR TYPE 2 DIABETES**
Type 2 diabetes mellitus is a public health problem of epidemic proportions and its prevalence is on the rise.

The metabolic syndrome is a powerful risk factor for Type 2 diabetes, stronger than for CVD. [82]

A meta-analysis of 16 cohorts showed that the presence of the MS increases the risk of developing diabetes by about 5 times. [83]

- Framingham Heart Study -- nearly 7 times the risk over 8 years [84]
- San Antonio Heart Study -- 3.3 times the risk over 7 to 8 years [85]
- Insulin Resistance Atherosclerosis Study -- 3.4 to 5.4 times the risk over 5-6 years. [86]
- Prospective study of general practices in 24 British towns -- 3.6 times the risk over 20 years. [87]
- Community-based study, normal-weight subjects with the Metabolic Syndrome had 4 times the risk of developing Type 2 diabetes; obese with the syndrome had 10 times the risk of obese without the syndrome over 11 years. [88]
- Hypertensive patients with the syndrome -- nearly 8 times risk of developing Type 2 diabetes over 4 years, and hypertensive patients who developed the syndrome over the 4 year study period were 4 times as likely to develop Type 2 diabetes. [89]
- In samples from the general population, the presence of the metabolic syndrome increased the risk for Type 2 diabetes by 3 times. [90]

The greater the number of components of the syndrome present, the greater the risk of developing Type 2 diabetes compared with the subjects without the MetS.

- Insulin Resistance Atherosclerosis Study (IRAS), the 5-year probability of developing Type 2 diabetes by number of components of the MetS was: no components = 5%; one = 11%; two = 18%; three = 37%; four = 45%; and all five = 50% [91]
- 1.58 times the risk for one component, 2.48 times the risk for two components, 3.10 times the risk for three components (diagnosis), and 5.22 times the risk for those with four components. [92]
- The probability of developing CVD or DM2 over 20 years increased from 11.9% in those with no abnormalities to 31.2% in those with 3 abnormalities to 40.8% in those with 4 or 5 abnormalities. [93]
- The relative risks of incidence of type 2 diabetes for the presence of 1,2,3, and > or =4 components, were, respectively, 1.92, 4.36, 6.44, and 15.08. [94]

This data suggests that the metabolic syndrome accounts for approximately half of new cases of Type 2 diabetes. [90,95]

**Chronic Kidney Disease is another important effect of the MS**
The metabolic syndrome is associated with an increased risk for CKD and albuminuria. [96]
- An analysis from the NHANES database showed that chronic kidney disease increases with number of components of the metabolic syndrome.

## 5. ETIOLOGY AND MECHANISMS

The 2 major underlying risk factors for the metabolic syndrome are obesity and insulin resistance. [97]
- Exacerbating factors are physical inactivity, advancing age, and endocrine and genetic factors.
- Associated hyperinsulinemia, hyperglycemia, and elevated adipokine levels (adipose cytokines) lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease.

The simple fact that over 90% of cases of metabolic syndrome in obese people are reversed after weight reduction surgery suggests that obesity is the driving force. [21]
- There is agreement that full expression of the syndrome depends on complex interactions between multiple possible genetic determinants (still largely unknown) and lifestyle habits.

Chronic energy imbalance seems to be the underlying problem. But the resulting pathophysiology is complex and not well understood. Adipocyte hypertrophy and hyperplasia, endoplasmic reticulum stress, and mitochondrial dysfunction are involved. [98]
- lead to increased intracellular and systemic release of adipokines, free fatty acids, and inflammatory mediators that cause adipocyte dysfunction and induce adverse effects in the liver, pancreatic β-cells, and skeletal muscle as well as the heart and vascular beds.

Insulin resistance is a generalized metabolic disorder characterized by inefficient insulin action in its primary targets -- skeletal muscle, liver and adipocytes. [99]
- It has long been recognized as an important metabolic link between the components of metabolic syndrome. [100]
Adipose tissue is exquisitely insulin sensitive in the healthy state, switches rapidly between fat uptake and fat release; it becomes dysregulated, and unresponsive in hyperinsulenic state.

Skeletal muscle is the primary tissue of insulin stimulated glucose uptake, disposal, and storage. Consequently it has a significant role in insulin sensitivity, as well as energy balance. Caloric excess, obesity and physical inactivity lead to skeletal muscle insulin resistance.

Recently, many nuclear receptors expressed in skeletal muscle have been shown to improve glucose tolerance, insulin resistance, and dyslipidemia.

The mechanisms that underlie the development of insulin resistance may not be completely understood, but the causes of the syndrome are -- obesity and too little physical activity, coupled with genetic factors. Obesity and inactivity both cause insulin resistance, and reduced utilization of glucose.

A 600% difference in glucose uptake between the most insulin-sensitive and the most insulin-resistant persons has been reported. Approximately 25% of this variability has been attributed to differences in adiposity, another 25% to differences in fitness, and the remaining 50% to genetic differences.

Studies show that lifestyle factors are generally more important than genetic factors. Japanese-American men show a more rapid and intense progression of atherosclerosis than native Japanese in Japan, and they have three times the prevalence of the MS. Differences are not as pronounced in women.

The Crucial Role of Abdominal Obesity

Increasing evidence points to visceral, or abdominal, obesity as the key link between genes and insulin resistance and the development of the syndrome. How fat is distributed, i.e., the apple shape vs the pear shape, is largely genetically determined; risk is much higher with the apple shape (hence, the importance of waist circumference as a primary criteria).

Visceral, or abdominal, adipocytes are different than peripheral adipocytes in important ways:
- As they expand they become more and more metabolically active,
- They produce numerous proteins, called adipokines, that have wide ranging biological activity, including key roles in the regulation of energy balance, lipid and glucose metabolism, angiogenesis, vascular and blood pressure regulation and insulin resistance.
- Production and release of adipokines becomes dysregulated as the adipocytes expand; they all increase except one -- adiponectin.
- Lipolytic activity increases -- more free fatty acids are released into the blood (see below).
- Increased levels of adipokines contributes to systemic inflammation, hence, atherogenesis.
- These adipocytes have changed the view of adipose tissue -- from passive energy storage cells to a metabolically active endocrine organ.
- Mounting evidence suggests that the repertoire of actions and reactions of adipocytes contributes to whole-body glucose and energy homeostasis, the control of blood pressure, immune-system function, haemostasis and atherosclerosis.

Adipokines

The list of substances that are produced and released by fat cells continues to grow. Leptin was the first to be recognized and remains the most recognizable; it is involved in regulating appetite, satiety, and fuel metabolism. Leptin was once thought to offer a cure for obesity, based on animal studies, but results have been far less impressive in studies with humans.

Adiponectin is the new hope, differs from other adipokines in that its production and concentrations are actually decreased in insulin resistant subjects; increasing levels improve insulin sensitivity; is increasingly considered a major factor in obesity-related insulin resistance and atherosclerosis.
Resistin increases insulin resistance and may stimulate glucose output from the liver. [110]

Other adipokines include TNF-α, IL-6, IL-1beta (interleukin 1beta), angiotensinogen, plasminogen activator inhibitor-1, acylation stimulating protein, tissue factor, monocyte chemoattractant protein-1, macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor, transforming factor β, adipsin, visfatin and haptoglobin. [110,111]

They are all increasingly produced by fat cells when they expand and become more active metabolically.

A number of these are linked to inflammation and the inflammatory response.

Data from the Framingham Offspring Study shows that adverse levels of adipokines (lower adiponectin, and higher resistin and TNF alpha) are associated with insulin resistance in individuals at low or high diabetes risk. [112]

Increased FFA Flux

Increased plasma levels of free fatty acids (FFA) occur in states of insulin resistance such as the metabolic syndrome. [113]

High levels of plasma FFA seem to play an important role for the development of insulin resistance but the mechanisms involved are not clearly understood. One effect is that insulin-stimulated glucose uptake and metabolism is impaired in skeletal muscle.

FFA compete with glucose for substrate utilization in skeletal muscle and block insulin signalling pathways; this reduces insulin sensitivity and glucose disposal in muscle and liver, causing an increase in blood glucose; insulin secretion is stimulated, resulting in hyperinsulinaemia -- a key feature of the insulin-resistance syndrome.

Leads to accumulation of triglyceride in muscle and liver, which further depresses insulin action in these tissues and increases the output of apo B-containing lipoproteins. [114]

The Metabolic Syndrome is progressive

Glucose metabolism becomes progressively disrupted as insulin resistance develops; hyperinsulinemia gives way to fasting hyperglycemia, then IGT and finally Type 2 diabetes.

Borderline risk factors progress to categorical risk factors. [115]

Several facets of the metabolic syndrome -- hypertension, hyperglycemia, and dyslipidemia -- stimulate the generation of free radicals, which impair the activity of nitric oxide, causing reduced endothelial-derived vasorelaxation (endothelial dysfunction). [116,117]

Abnormalities in the vasculature begin early in the process, along with subtle abnormalities in glucose metabolism.

The degree of endothelial dysfunction increases progressively from normal to first-degree relatives of diabetic persons to people with impaired glucose tolerance to those with type 2 diabetes. [118]

Visceral fat is also a key regulator of inflammation.

Abdominal obesity is characterized by a state of chronic mild inflammation.

Large clinical studies have shown that CRP, as a marker of inflammation, increases with the number of components of the MS, as well as Type 2 diabetes. [109]

Adipocytes directly promote the inflammatory state through the secretion of a growing list of cytokines (adipokines) that promote inflammation. [119]

This inflammation appears to be a crucial step in the emergence of insulin resistance, and is increasingly considered to be important in the development of diseases linked to obesity, particularly Type 2 diabetes and the metabolic syndrome. [119-121]

There is increasing evidence from nearly every internal medicine subspecialty that adipocytes and adipokines are involved in primary inflammatory processes and diseases. [122]

Effects of inflammation

Interferes with normal insulin signalling. [109]
promotes thrombosis, a process that underlies acute coronary event and stroke. [123]
renders HDL proinflammatory instead of anti-inflammatory. [124]

Relation to disease
Many epidemiologic studies have shown associations between inflammation markers and diabetes, the most consistent being for leukocytes, the strongest being for CRP. [125]
Consistent with this relation, inflammation markers have also been shown to predict conditions present in the prediabetes state such as weight gain, hypertension, gestational diabetes, and declining insulin sensitivity and the Metabolic Syndrome. [126]
Elevated levels of CRP are also associated with increased risk for CVD and diabetes. [126]
Increasing severity of metabolic syndrome is also associated with increasing CRP. [127]

Importance of using waist circumference to assess obesity risk
Waist circumference is a key marker for the metabolic syndrome because it is a measure of visceral adiposity -- the type of body fat that is very metabolically active and that contributes to health risks. [128]
Visceral abdominal fat is the most significant predictor of the presence of metabolic syndrome, particularly in normal-weight individuals. [128]
For a given WC, overweight, obese and normal-weight persons have been shown to have comparable health risks. [129]

It is a simple measure for identifying insulin resistance. [130]
At any BMI, greater waist circumference predicts increased risk of the presence of the MS. [131]
In young men it is independently associated with insulin resistance; helps identify sub-groups of overweight or obese young men at higher metabolic risk. [132]

It has the strongest relation to inflammation (increased CRP levels) of the five Metabolic Syndrome criteria. [133]
And, it is superior to BMI for predicting future myocardial infarctions. [134]

Impact of Sedentary Lifestyle
Cross-sectional and prospective studies generally support that levels of physical activity and fitness are inversely related to the prevalence of this syndrome. [135]
Sedentary behaviors, such as excessive time spent watching television or using a computer, are significantly associated with an increased risk for this syndrome.
Compared to subjects who viewed TV < 14 hr/week, those who viewed TV > 20 hr/week had a 1.5-fold risk for men and a 1.9-fold risk for women of having metabolic syndrome, after adjusting for physical activity and other covariates. [136]

Some suggest that low cardiorespiratory fitness should be considered a feature of metabolic syndrome.
Vo(2max) has a strong, inverse, and graded association with the risk of metabolic syndrome. Men and women in the lowest third of Vo(2max) had 10- and 11-fold higher risks and those in the middle third had 3- and 5-fold higher risks (P < 0.001 all) of metabolic syndrome than those with the highest Vo(2max) after multivariable adjustments. [137]

6. TREATING THE METABOLIC SYNDROME
People with the Metabolic Syndrome require attention to risk factors for both atherosclerotic cardiovascular disease and type 2 diabetes. There are two objectives in managing the syndrome:
1. to reduce the underlying causes (i.e., obesity and physical inactivity), and
2. to treat associated risk factors, including separate drug therapy when appropriate. [138]
The first line treatment is lifestyle therapy because it can improve all aspects of the syndrome. But, as it progresses, drug therapy directed at individual risk factors may be needed. [139]
According to the NCEP ATP III – the presence of the syndrome is an indication for intensive lifestyle modification. [NCEP]

- Weight loss, increased physical activity, and an anti-atherogenic diet can improve all of the metabolic abnormalities without pharmaceutical intervention. [140]

There are currently no drugs specifically for the Metabolic Syndrome. [140]

- Drugs for insulin resistance and the MS are being studied.
- Some show promise (e.g., thiazolidinediones) but await additional research.

But drug therapy is often needed to control risk factors when lifestyle change alone is not enough. [140]

Weight loss has a huge impact in improving the risk factors of the metabolic syndrome. Several studies have shown that losing just 7% to 10% of initial body weight is sufficient to improve waist circumference, elevated triglycerides and low HDL-cholesterol, trunk fat, and plasma glucose. [141]

**Importance of a Multi-Faceted Approach**

There is growing consensus of the importance of a multifaceted approach, tailored to the patient's unique risk profile -- treating all risk factors together, early and aggressively. [117]

- Includes global cardiovascular risk assessment.
- Weight reduction and increased physical activity are always the foundation. [142]
- With drug therapy, attention to the varying effects that agents of different therapeutic classes have on other cardiovascular and metabolic parameters.

A CME program summarizes the key aspects of treatment for the prevention of cardiovascular and renal disease in patients with the metabolic syndrome: [143]

- Quit smoking, if a smoker -- obviously extremely important in view of already heightened risk
- A diet that replaces bad fats and carbs with good ones, with increased fiber; in other words, more of a Mediterranean diet, or the DASH diet from the NIH.
- Increased exercise -- such as walking 30 minutes every day.
- Aspirin therapy, and perhaps other platelet antagonists, for the pro-thrombotic effects.
- Lipid control -- focuses on reducing triglycerides and apo B, raising HDL and lowering LDL; the LDL goal has become more stringent in the presence of the Metabolic Syndrome -- < 70 mg/dL vs < 100 mg/dL without it; often requires a combination approach.
- Blood pressure control -- also often requires a combination medication approach, and
- Good control of glycated hemoglobin, < 7% by ADA standards; < 6.5% by AACE standards; the lower the better, in view of the early appearance of atherosclerotic changes with the syndrome.

Simultaneous management of multiple risk factors has the potential to greatly reduce the incidence of CVD in individuals with the metabolic syndrome. [144]

**Lifestyle Therapy -- The Cornerstone of Treatment**

The most indisputable fact about the Metabolic Syndrome is the importance of lifestyle changes in managing it. This is:

- "the most effective therapeutic intervention for patients with the metabolic syndrome". [145]
- "the best available option for treating the metabolic syndrome". [146]

There is abundant evidence that this approach can reduce the likelihood of developing type 2 diabetes. [147]

- In a meta-analysis, lifestyle interventions reduced diabetes by approximately one-half and pharmacologic interventions by approximately one-third.
- Major lifestyle studies included the Finnish Diabetes Prevention Study (DPS) [148] and the U.S. Diabetes Prevention Program (DPP) [149], both with reductions in development of diabetes by 58%.
- Diabetes Prevention Program evaluated effectiveness of lifestyle approach to prevent Type 2 diabetes in obese -- was stopped early because results were indisputable:
  - 2 years -- 5% of lifestyle group vs 22% of control developed diabetes,
  - 4 years -- 20% (lifestyle) vs 37% (control) developed diabetes. [149]
The Finnish Diabetes Prevention Study evaluated diet and exercise intervention in people with impaired glucose tolerance. After 6 years, fewer than 20% of diet/exercise group vs greater than 40% of control developed type 2 diabetes [148].

There is also growing evidence on improving the clinical status of patients with the syndrome.

- A significant reduction in the prevalence of metabolic syndrome (OR 0.6) and abdominal obesity (0.5) was observed in the previously mentioned Finnish Diabetes Prevention Study. [150]
- A general recommendation-based program of lifestyle intervention carried out by trained professionals was compared to standard unstructured information given by family physicians. The result: after one year, the lifestyle intervention significantly reduced the metabolic syndrome (OR = 0.3), as well as central obesity (OR = 0.3), hypertriglyceridemia (OR = 0.5), and diabetes (OR = 0.2) [151]
- The combination of diet and exercise interventions was significantly more effective than either diet or exercise alone in the treatment of the metabolic syndrome after a one year study. Two out three cases were reversed with the combination vs only about 1 in 3 in each of the other groups. [152]

**Exercise**

Exercise has many positive effects in people with metabolic syndrome – improving insulin action, glucose metabolism, aerobic metabolism, mitochondrial density, and respiratory chain proteins. [153]

Randomized controlled trial evidence shows that exercise training in people with the MS or IGT:

- Increases insulin sensitivity,
- Decreases blood pressure, if elevated,
- Reduces triglycerides, increases HDL,
- Reduces inflammation,
- Improves endothelial function [155]

Almost all physical activity has a positive effect on insulin action, but moderate intensity, daily activity seems best. A significant part of the positive effect comes from the last bout of activity, hence the need for daily activity. [156]

- 30 minutes brisk walking 3-7 times per week over 6 months reversed insulin resistance in sedentary insulin resistant individuals with no change in diet or weight. [157]
- Small increases in activity and fitness improved clustered metabolic risk in the ProActive cohort of at-risk individuals. [158]
- Both an increase in overall physical activity and an increase in cardiorespiratory fitness improve the entire cluster of metabolic abnormalities. [154]
- Adding some resistance exercise to aerobic exercise can provide additional benefits. [159]
- A modest amount of moderate-intensity exercise, with no change in diet, significantly improved MS and supported the recommendation of 30 minutes of moderate-intensity exercise every day. [160]
  - Increasing the volume of exercise, i.e., more than 30 minutes per day, had greater benefits than increasing the intensity of exercise.

A physician should be consulted before beginning a new physical activity program for people with chronic diseases, such as cardiovascular disease and diabetes mellitus, or for those who are at high risk for these diseases. Experts also advise men over age 40 and women over age 50 to consult a physician before they begin a vigorous activity program. [AHA/ACSM Guidelines, see Resources]

Just becoming less sedentary has a positive effect on the syndrome.

- The Australian Diabetes, Obesity and Lifestyle study has shown that avoiding prolonged uninterrupted periods of sedentary time, especially sitting, has a favorable effect on waist circumference, BMI, triglycerides, and 2-h plasma glucose. [161]
The Nurses' Health Study has shown the importance of both reducing sedentary activity and increasing physical activity. Sedentary behaviors, especially TV watching, were associated with significantly elevated risk of obesity and type 2 diabetes, whereas even light to moderate activity was associated with substantially lower risk. [162]

Exercise can be as simple as brisk walking for 30 minutes a day, or as complicated as a combination of aerobic and resistance training with a professional trainer. [163]

- First goal is to just become more active -- look for ways to stand more, walk more, just be more active
- Then, begin light exercise, such as walking a mile in about for 20-30 minutes; build up to doing this most days of the week,
- Then, begin to walk a little faster; moderate exercise is considered the equivalent of walking 2 miles in 30 minutes most days of the week,
- Then, begin adding a few longer walks, such as 45 minutes, a couple of times a week,
- Then, add some calisthenics, stretching or light exercises with weights, such as machines or dumbbells.
- Each step builds on the one before it; as the patient gets stronger, he or she will naturally become more active.

**Diet Changes**
The epidemic of the Metabolic Syndrome has been seen by some as the unwanted result of the dietary low fat crusade that has dominated the past 50 years. [164]

- Fat intake has dropped but obesity and the metabolic syndrome have risen.
- The problem is that low fat diets tend to be high in carbohydrates, and there is evidence that such diets may increase triglycerides and reduce HDL in susceptible people. [165]
- The 2006 AHA scientific statement on diet and lifestyle recommendations recommends a moderate fat intake for the metabolic syndrome. [166]

There is no single diet currently recommended for people with the Metabolic Syndrome, BUT there is evidence to support a Mediterranean style diet as the best approach. [21]

- A systematic review of 35 studies of the effects of the Mediterranean diet showed favorable effects on lipoprotein levels, endothelial vasodilatation, insulin resistance, metabolic syndrome, antioxidant capacity, myocardial and cardiovascular mortality, and cancer incidence in obese patients and in those with previous myocardial infarction. [167]
- Analyses from the Nurses' Health Study suggest that over 80% of coronary heart disease, 70% of stroke, and 90% of type 2 diabetes can be avoided by healthy food choices that are consistent with the traditional Mediterranean diet, along with regular physical activity and not smoking. [168]
- A Mediterranean style diet reduced the prevalence of the syndrome by nearly 50% over a low fat diet. [169]
- The Dietary Approach to Stop Hypertension (DASH) diet, which is similar to a Mediterranean diet, reduced the prevalence of the metabolic syndrome by 35% compared with a control diet. [170]
- A dietary pattern that included frequent intake of vegetables, fruits, fish, pasta and rice and low intake of fried foods, sausages, fried fish, and potatoes was associated with a better metabolic profile. [171]

Translated the Mediterranean diet means:

- Eating more good fats (olive oil, nuts, fish oils) and fewer poor fats (saturated and trans -- fast foods, packaged baked goods) and,
- More good carbohydrates (whole grains, vegetables, fruits -- high in fiber and antioxidants) and fewer bad carbohydrates (refined sugars, candy, soft drinks, processed and packaged foods),
- Choosing leaner sources of proteins and low fat dairy.

The importance of good fats and whole grains:
There is growing evidence that the type of fat in the diet plays an important role in the development of insulin resistance. [172]
Higher levels of saturated fats impair the action of insulin, while polyunsaturated fatty acids, especially omega-3 and -6, improve insulin sensitivity, hence the beneficial effects of adding a fish oil supplement.

Omega-3 fatty acids in fish oils help reduce triglycerides and increasing HDL, and have the added benefit of antioxidant properties.

Fatty acids have also been shown to alter gene expression in cells, in particular the peroxisome proliferator-activated receptor-gamma2 gene, adding to this multifaceted connection.

Substituting whole grains for refined grains in the same hypocaloric diet in people with metabolic syndrome resulted in a significantly greater decrease in percentage body fat in the abdominal region, and a significantly greater reduction in inflammation. [173]

Increased whole grain and cereal fiber intake was also associated with a reduced risk of developing the metabolic syndrome in the Framingham Offspring Study. [174]

In middle-aged adults, soft drink consumption is associated with a higher prevalence and incidence of multiple metabolic risk factors. Consumption of ≥1 soft drink per day was associated with nearly 1.5 times the risk of developing metabolic syndrome. [175]

Emerging evidence also suggests that increased consumption of fructose may also be a factor in the growing rates of obesity and the metabolic syndrome. [176]

The Glycemic Index and Glycemic Load have received attention in relation to the Metabolic Syndrome.

The GI of a food is a value based on the average increase in blood glucose levels occurring when a 50 g carbohydrate portion of that food is consumed. The GL accounts for the amount of carbohydrate per serving.

However, evidence suggests that the importance of low GI or GL diets in relation to the metabolic syndrome has yet to be established. One of the reasons is that the diets used in the intervention studies frequently not only differed in GI or GL, but also in fiber, protein and/or fat content.

In some prospective cohort studies, effects of GI or GL disappeared after correcting for fiber intake. [177]

The Atherosclerosis Risk in Communities (ARIC) study found that long term consumption of a Western dietary pattern, especially including meat, fried foods, and diet soda, increased the risk of developing the Metabolic Syndrome. [178]

The Whitehall II study confirmed this -- a dietary pattern with high consumption of diet soft drinks, onions, sugar-sweetened beverages, burgers and sausages, crisps and other snacks, and white bread and low consumption of high-fiber breakfast cereals, jam, French dressing/vinaigrette, and whole wheat bread was associated with the development of insulin resistance and type 2 diabetes. [179]

**Pharmacologic Therapy**

The goal is to prevent, or at least slow, the development of cardiovascular disease and type 2 diabetes.

In view of the difficulties of long term weight loss and adherence to diet and exercise regimens, drug therapy is often needed. [180]

There are currently no specific drugs to treat insulin resistance or the Metabolic Syndrome in general, but there likely will be in the not too distant future. [181]

Keep abreast of this line of research (see drugs in the pipeline below).

There are, obviously, effective drug therapies to treat the individual conditions, including:

- Prevention of type 2 diabetes, hyperglycemia
- Dyslipidemia
- Hypertension
- Increased coagulation
- Decreased fibrinolysis

Pharmacologic therapy for lipids and blood pressure, at minimum, will eventually be needed for most people with the Metabolic Syndrome. [182]
Drugs for the Prevention of Type 2 diabetes
This is a primary goal because of widespread and devastating complications that result, along with the fact that the Metabolic Syndrome increases risk for diabetes so much.

- Beyond diet and exercise, several oral anti-diabetic agents have been shown to reduce the development of diabetes in patients with IGT, when the syndrome has progressed to that point.
- These include metformin, acarbose and troglitazone. [183]
  - Metformin decreases the amount of glucose made by the liver while increasing glucose uptake by target tissues. HbA1c reduction of 1% to 2% can be expected.
  - Acarbose (an Alpha-Glucosidase Inhibitor) and Troglitazone (a thiazolidinedione) are still being investigated for use with the MS
  - More interestingly, multiple large prospective studies have also reported a reduction in the development of type 2 diabetes with anti-hypertensive therapy using ACE inhibitors and angiotensin receptor blockers (ARBs). [184]
  - A meta-analysis of 12 randomized controlled clinical trials showed that ACE inhibitors and ARBs reduced the incidence of newly diagnosed diabetes by 27% and 23%, respectively. [184]

Drugs for Dyslipidemia
The first priority is to reduce LDL cholesterol to the new lower limit of below 70 mg/dL, owing to the highly increased risk of CVD.

- Management should allow for statins in virtually all cases. [182]

Next priority is to address the more typical lipid abnormalities seen in patients with the metabolic syndrome -- higher triglyceride and apolipoprotein B levels, lower HDL cholesterol and apolipoprotein A-I levels, and smaller, denser, more numerous LDL cholesterol particles. [182,185]

- Many will still have elevated TGs, low HDL, and many will still have elevated levels of small, dense LDL, even after statin therapy.

Therefore, combination therapy is often necessary.

A recent European Consensus Panel recommends the combination of nicotinic acid and a statin, with lifestyle modification, as a useful strategy to lower CHD risk in patients with metabolic syndrome. [186]

- Nicotinic acid can raise HDL-C (by up to 29% at clinically recommended doses). It also substantially reduces triglycerides and LDL-C, and promotes a shift from small, dense LDL to larger, more buoyant LDL particles.
- Preliminary clinical data suggest that combining nicotinic acid with a statin will produce a greater reduction in cardiovascular risk in patients with diabetes and metabolic syndrome than statin monotherapy alone.
- Prolonged-release nicotinic acid with improved tolerability compared with previous formulations may have obvious advantages for use in this setting.

Fibrates, such as gemfibrozil and fenofibrate, lower triglyceride and raise HDL cholesterol levels. [182]

- The mechanisms are not completely understood, but one is the upregulation of the enzyme, lipoprotein lipase, which hydrolyzes TGs and VLDLs; the result is that there is more efficient conversion of VLDL to remnant particles, a reduction in TGs and improved removal of these remnant lipoproteins.
- Gemfibrozil is not recommended in combination with statins because of an increased risk of rhabdomyolysis.

Niacin derivatives, especially extended-release niacin, may also be effective in lowering LDL cholesterol and triglycerides and increasing HDL cholesterol. [182]

- Niacin essentially puts the brakes on adipocytes, reducing the flux of fatty acids, one of the primary drivers for hyperlipidemia in insulin-resistant patients.
- The dose needs to be titrated slowly and should be given with immediate-release aspirin to prevent flushing reactions. At higher doses, they may cause deterioration in glucose control.
**Statins**
Drugs of choice when LDL cholesterol is elevated (above the new aggressive goal of 70 mg/dL). [187]
- Can improve other aspects of dyslipidemia as well
- In patients with the metabolic syndrome, rosuvastatin 10 mg improved LDL cholesterol (-47%), non-HDL cholesterol (-43%), non-HDL cholesterol/HDL cholesterol ratio (-47%), apolipoprotein B (-37%), apolipoprotein B/apolipoprotein A-I ratio (-40%), triglycerides (-23%), apolipoprotein A-I (+7%), and HDL cholesterol (+10%) in a manner similar to that in hypercholesterolemic patients who did not meet these criteria. [188]

Data from the Heart Protection Study (HPS) and the Collaborative Atorvastatin Diabetes Study (CARDS) have clearly shown that statins reduce the risk of cardiovascular events in diabetics (by 24% and 37%); has led to the wide spread belief that most diabetics as well as others at high risk for vascular events could benefit from statins regardless of age or initial serum lipids. [189]
- Cholesterol absorption inhibitors, such as ezemtimide, have been recently shown in the SANDS Trial to reduce carotid atherosclerosis is patients with diabetes [239].
- Ezemtimide is also indicated to lower apo B.

**Drugs for Hypertension**
Hypertension should be managed aggressively, with a target of 130/80 mm Hg or below.
- Multiple agents are usually required. [182]
- ACE inhibitors and ARBs have the additional advantage of preventing the deterioration of glucose tolerance. [182,183]

**Anti-thrombotic**
Aspirin therapy should be administered if the cardiovascular risk is high. [187]

**Drugs in the Pipeline for the Metabolic Syndrome**
The thiazolidinedione class of "insulin-sensitizing" agents appears to show great promise for the future. [190]
- These drugs directly target insulin resistance.
- Rosiglitazone (Avandia) and Pioglitazone (Actos) are examples.
- Pioglitazone, alone and with metformin, has been shown to improve glycaemic control and lipid profiles in patients with the metabolic syndrome in combined data from four worldwide randomized, multicenter, double-blind studies.
- A reduction in HbA1c of 1-2% can be expected.
- Close monitoring of liver function tests is advised since hepatotoxicity is the main serious adverse effect. These drugs may take a few weeks before they affect blood glucose levels.

Another class of drugs being intensively studied is the Alpha-Glucosidase Inhibitor group. [191]
- These drugs block the alpha-glucosidase enzymes in the intestines that are responsible for the breakdown and absorption of carbohydrates during digestion; blocking the enzymes thus slows absorption of glucose into the blood.
- Acarbose (Precose) and Miglitol (Glyset) are examples
- HbA1c reduction in the range of 0.5-1% can be expected. Side effects are typically limited to upset stomach.
- The STOP-NIDDM study (study to prevent non-insulin-dependent diabetes mellitus) showed a 49% reduction of cardiovascular events in patients with IGT treated with acarbose, compared with placebo.
- Furthermore, a retrospective meta-analysis of seven placebo-controlled long-term-studies of acarbose in patients with Type 2 diabetes showed a reduction of cardiovascular events of 41%.
7. GUIDELINES

Diagnosis and Management of the Metabolic Syndrome -- from the American Heart Association/National Heart, Lung, and Blood Institute, 2005 [4]

http://circ.ahajournals.org/cgi/content/full/112/17/e285#TBL1

RECOMMENDATIONS:

Diagnosis: Use the NCEP ATP III criteria

Lifestyle Modification:

Weight loss:
- Goal: Reduce body weight by 7%–10% during first year of therapy. Continue weight loss with goal to ultimately achieve desirable weight (BMI <25 kg/m²)
- Approach: Encourage weight maintenance/reduction through balance of physical activity, caloric intake, and formal behavioral programs to maintain/achieve waist circumference of <40 inches in men and <35 inches in women. Aim initially at slow reduction of 7%–10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.

Physical activity:
- Goal: Regular moderate-intensity physical activity; at least 30 min of continuous/intermittent (preferably 60 min) 5 d/wk, but preferably daily
- Approach: If established CVD, assess risk with detailed physical activity history and/or exercise test, to guide prescription. Encourage 30–60 min moderate-intensity aerobic activity (eg, brisk walking), preferably daily, supplemented by increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, household work). Higher exercise times achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients.

Diet:
- Goal: Reduced intakes of saturated fat, transfat, cholesterol
- Approach: Saturated fat <7% of total calories; reduce trans fat; dietary cholesterol <200 mg/d; total fat 25%–35% of total calories. Most dietary fat should be unsaturated, simple sugars should be limited.

Therapy for specific risk factors:

Atherogenic dyslipidemia:
- Primary target: LDL-C. Reduce LDL-C levels to ATP III goals
  - For elevated LDL-C: Give priority to reduction of LDL-C over other lipid parameters.
  - Achieve LDL-C goals based on patient’s risk category:
    - High risk: <100 mg/dL (optional <70 mg/dL for high-risk patients)
    - Moderately high risk: <130 mg/dL (optional <100 mg/dL)
    - Moderate risk: <130 mg/dL
    - Lower risk: <160 mg/dL
- Secondary target: Non-HDL-C. If TG ≥200 mg/dL, reduce non-HDL-C to ATP III goals (after attaining LDL-C goals)
  - If TG ≥200 mg/dL, goal for non–HDL-C for each risk category is 30 mg/dL higher than for LDL-C.
  - If TG ≥200 mg/dL after achieving LDL-C goal, consider additional therapies to attain non-HDL-C goal.
- Tertiary target: HDL-C if low, after attaining non-HDL-C goal, raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia
  - If HDL-C is low after achieving non–HDL-C, either lifestyle therapy can be intensified or drug therapy can be used for raising HDL-C levels, depending on patient’s risk category.
Elevated BP:
- **Goal:** Reduce BP to <140/90 mm Hg (or <130/80 mm Hg if diabetes is present).
  - For BP ≥120/80 mm Hg: Initiate or maintain lifestyle modification via weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products in all patients with metabolic syndrome.
  - For BP ≥140/90 mm Hg (or ≥130/80 mm Hg if diabetes is present), add BP medication as needed to achieve goal BP.

Elevated glucose:
- **Goal:** For impaired fasting glucose (IFG), delay progression to type 2 diabetes mellitus. For diabetes, hemoglobin A1C <7.0%.
  - For IFG, encourage weight reduction and increased physical activity.
  - For type 2 diabetes, 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:
- **Goal:** Reduce thrombotic and fibrinolytic risk factors
  - For high-risk, initiate and continue low-dose aspirin therapy; with CVD, consider clopidogrel if aspirin is contraindicated.
  - For moderately high-risk patients, consider low-dose aspirin prophylaxis.

Proinflammatory state:
- **No specific therapies beyond lifestyle therapies**

**Physical Activity – from the American College of Sports Medicine and the American Heart Association, 2007** [192]
The minimum physical activity recommendations to promote and maintain health in adults 18-65 include:
- At least 30 minutes of moderate-intensity aerobic activity five days a week. Moderate activity is equivalent to a brisk walk that causes the heart to beat faster. Can be all at once or in segments of at least 10 minutes, OR
- At least 20 minutes of vigorous activity three days a week. Vigorous activity, such as jogging or running quickly, raises the heart rate and causes you to breathe quickly, AND
- At least two non-consecutive days of muscle-strengthening exercise each week. Eight to 10 exercises per session with a weight that allows 8-12 repetitions of each exercise. May include a progressive-weight training program, exercises or calisthenics that involve weight-bearing activity or activities such as stair climbing.

To lose weight or further reduce the risk for premature chronic health conditions and mortality requires exceeding these minimum amounts.

**Diet – U.S. Preventive Services Task Force, 2003** [193]
Intensive behavioral dietary counseling is recommended for adult patients with hyperlipidemia and other known risk factors for cardiovascular and diet-related chronic disease.
- Two approaches appear promising in primary care settings:
  - (1) medium-intensity face-to-face dietary counseling (two to three group or individual sessions) delivered by a dietitian or nutritionist or by a specially trained primary care physician or nurse practitioner, and
  - (2) lower-intensity interventions that involve 5 minutes or less of primary care provider counseling supplemented by patient self-help materials, telephone counseling, or other interactive health communications.
- The largest effect of dietary counseling has been observed with more intensive interventions (multiple sessions lasting 30 minutes or longer) among patients with hyperlipidemia or hypertension, and among others at increased risk for diet-related chronic disease.
- The 5-A behavioral counseling framework is supported:
  - **Assess** dietary practices and related risk factors,
  - **Advise** to change dietary practices,
Examples of behavior counseling interventions include teaching self-monitoring, training to overcome common barriers to selecting a healthy diet, helping patients to set their own goals, providing guidance in shopping and food preparation, role playing, and arranging for intra-treatment social support.

Office-level systems supports (prompts, reminders, and counseling algorithms) have been found to significantly improve the delivery of appropriate dietary counseling by primary care clinicians.

The USPSTF concluded that such counseling is likely to improve important health outcomes.

Treatment of the Metabolic Syndrome – Finnish Medical Society, 2007 [194]

Treatment of the Metabolic Syndrome (MS) is principally non-pharmacological and based on lifestyle changes. This approach has been shown to have an excellent effect, for example in the prevention of diabetes (DPS Study) (Tuomilehto et al., 2001; Knowler et al., 2002) [A].

Lifestyle changes are the only treatment form which have an effect on all the components of the syndrome, and not employing this treatment should be considered ethically wrong.

Non-Pharmacological Treatment includes:

- Increasing physical activity
- Weight reduction
- Dietary changes: increased intake of fiber and decreased intake of fat (particularly saturated fat) and rapidly metabolized carbohydrates (highly refined); salt restriction
- Cessation of smoking
- Limit alcohol intake to a moderate level

Drug Treatment:

- Drug treatment for the entire syndrome does not exist; treatment consists of managing the individual components.
- Unless contraindicated, all patients with MS should be prescribed low dose aspirin.
- The treatment of hypertension should not contain drugs that worsen insulin resistance, such as non-selective beta-blockers and high-dose diuretics, unless other reasons (secondary prevention of myocardial infarction) warrant their use. The first-line drugs for the treatment of hypertension are:
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin-II receptor antagonists (losartan, valsartan, eprosartan, candesartan)
  - Alpha1 receptor blockers
  - Calcium-channel blockers
  - Highly selective beta-blockers

- Dyslipidemia should principally be treated with statins bearing in mind that the patient has a high risk of coronary artery disease.
- Hypertriglyceridemia should be treated with fibrates if, in spite of non-pharmacological treatment, the triglyceride values are persistently >5.0 mmol/L. Hypertriglyceridemia in a patient with MS should be treated medically (statin or fibrate) if the level of triglycerides is >2.30 mmol/L and total-cholesterol/HDL-cholesterol ratio is higher than 5 or if HDL-cholesterol is lower than 0.9 mmol/L.
- Dysglycemia in a patient with MS should be treated with metformin or thiazolidine derivatives (pioglitazone or rosiglitazone) since these will not only improve the dysglycemia but will also have an effect on the other components of the MS. Insulin may also be used for the treatment of dysglycemia in a MS patient to achieve good diabetic control.
- Biguanides, acarbose, and guar gum may correct insulin resistance and are thus feasible as a first-line drug for an obese patient with type 2 diabetes.
- Orlistat or sibutramine may be indicated in MS if the BMI is >30 kg/m². These are anti-obesity drugs that also reduce the amount of visceral fat, in particular. However, the new endocannabinoid-receptor...
blockers are likely to provide the best benefit among pharmacotherapeutic alternatives. Rimonabant is an example of these drugs, and it has a positive effect on almost all the components of MS.

- Rimonabant should not be prescribed if the patient is concurrently in severe depression. It should be prescribed with caution and the patient should be carefully followed up if he/she has a history of depression.

**Follow-up:**
- Motivation and monitoring of lifestyle changes is of the utmost importance.
- The monitoring of a patient who requires drug treatment is the responsibility of a doctor. Regular appointments may often act as an important motivator.
- Monitoring of patients not on drug therapy may be carried out by a practice nurse. The following should be included in the follow-up: motivation of lifestyle changes, weight and waist circumference measurements, blood pressure readings, and checking of blood lipids and fasting blood glucose. A doctor should be consulted if:
  - Blood pressure repeatedly >140 mmHg and/or >90 mmHg
  - Total cholesterol: HDL-cholesterol ratio >5
  - Triglyceride values repeatedly >2.30 mmol/L
  - Plasma glucose is >7.8 mmol/L (fasting plasma glucose is >6.7 mmol/L
  - The patient develops symptoms of another illness (gout, etc.)

**Screening for metabolic syndrome in adults -- University of Texas at Austin, Family Nurse Practitioner Program** [195]


**Objectives:**
- Provides a dietary and nonpharmacologic treatment guideline for the management of metabolic syndrome
- To guide practice decisions that integrate medical, nutritional, and behavioral elements
- To promote self-management education that empowers the patient to take responsibility for day-to-day management

This guideline provides detailed step by step guidelines for the initial and follow-up encounters – assessment, clinical data, intervention (education, training, communication, etc), monitoring

**8. THE CHALLENGES**

**Under-recognition**
This increasingly important pro-inflammatory condition remains both under-recognized and under-treated.
- Growing evidence supports early intervention, but many physicians do not recognize the risk associated with it and fail to initiate early treatment. [196]

**Improving lifestyle change counseling rates**
Assisting patients to improve health-related behaviors is an important responsibility of caregivers, including physicians, nurses, health educators, and counselors.

From 1992 to 2000, diet and physical activity counseling took place in < 45 and 30%, respectively, of primary care physician visits by adults with CVD risk factors. [197]
- Physicians in primary care seldom have time to engage in such discussions and may be unsure how to discuss behavior change with their patients; [197-199]
- Non-physicians are generally the appropriate caregivers to assist patients in adopting healthy behaviors.
Suspecting the Metabolic Syndrome
Early recognition of the metabolic syndrome is vital because of its progressive nature. The earlier in the process that intervention occurs, the less intensive the treatment required and the greater the likelihood of success. [200]

The presence of obesity or hypertension in any patient warrants screening for the metabolic syndrome and diabetes because of the vascular risk.
- The syndrome is common in patients with hypertension, present in over half in an analysis of a cohort of nearly 13,000 subjects with diagnosed hypertension. [201]
- But primary care providers overlooked the Metabolic Syndrome in over half of those who had it. [201]
- Abnormal glucose metabolism, including previously undiagnosed impaired fasting glucose and diabetes, are often already present in patients with serious heart conditions. [202]

A number of other conditions also increase the risk of developing the MS; hence, they should stimulate assessment of it. These include:
- prior gestational diabetes,
- elevated uric acid levels,
- familial hypercholesterolemia,
- nonalcoholic fatty liver, or
- polycystic ovary syndrome in women of reproductive age [203,204]

Measuring Waist Circumference
More and more experts advocate the including waist circumference as a vital sign in clinic visits to document the presence of central obesity. [205]

To measure waist circumference: [4,206]
1. Locate upper edge of hip bone, the iliac crest, on each side
2. Place cloth measuring tape in a horizontal plane (parallel to the floor) around the abdomen at this level
3. Make sure the tape is snug but not so snug that it compresses skin
4. Take the measurement at the end of a normal exhalation. Patient should be cautioned not to pull in stomach. A wall chart is helpful to compare patient with standards.

There are other methods of measuring waist circumference – the narrowest or widest point, the umbilicus, midpoint between lowest rib and iliac crest, but a systematic review found that the site of measurement did not influence clinical outcomes. [207]
- More important is that the same method be used consistently so changes can be accurately documented.

Evaluate the Primary Criteria
The NCEP criteria for the metabolic syndrome was designed for use in clinical practice. The only lab work required is a standard fasting blood test. [2,4]

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>≥ 35 inches for women or ≥ 40 inches for men</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Systolic pressure ≥ 130 OR Diastolic pressure ≥ 85</td>
</tr>
<tr>
<td>Fasting triglycerides</td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td>Fasting HDL cholesterol</td>
<td>&lt; 50 mg/dL for women or &lt; 40 mg/dL for men</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 100 mg/dL</td>
</tr>
</tbody>
</table>

- Currently taking medication for blood pressure, triglycerides, HDL or hyperglycemia counts as criteria met.
Diagnosis and Coding
If 3 or more criteria are met, the diagnosis is confirmed: ICD-9 CODE 277.7 "Dysmetabolic syndrome X" [26]
- Record the diagnosis in the medical record

Assess Cardiovascular Risk
The gold standard for CVD risk assessment is the Framingham Risk Score: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof
- It estimates the probability of a cardiovascular event in the next 10 years.
- Need to know total and HDL cholesterol, systolic BP, smoking status, age, gender
- Determine risk level:
  - Low risk: 5% or less
  - Intermediate risk: 6% to 20%
  - High risk: > 20% [196]
- Some recommend use of 10% as lower end of intermediate range. [4]

Outline Treatment Needs
ABCDE: A Practical Approach to the Metabolic Syndrome in Primary Care
This strategy aimed at primary prevention of cardiovascular events in people with the Metabolic Syndrome was developed at the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease. [196]

<table>
<thead>
<tr>
<th>ABCDE Approach for Treating the Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Aspirin</td>
</tr>
<tr>
<td>All patients with ≥ 6% 10-yr risk (without contraindications)</td>
</tr>
<tr>
<td>B Blood Pressure Control</td>
</tr>
<tr>
<td>Goal is &lt; 130/80 if intermediate risk (≥ 6% 10-yr risk)</td>
</tr>
<tr>
<td>First line pharmacotherapy: ACEI or ACE</td>
</tr>
<tr>
<td>B-blockers, diuretics may inc risk of diabetes</td>
</tr>
<tr>
<td>C Cholesterol Management</td>
</tr>
<tr>
<td>LDL-C First line pharmacotherapy: Statins</td>
</tr>
<tr>
<td>Goal is &lt; 130 mg/dL if intermediate risk</td>
</tr>
<tr>
<td>Goal is &lt; 100 mg/dL if high risk</td>
</tr>
<tr>
<td>Non-HDL-C Statin intensification, Fenofibrate</td>
</tr>
<tr>
<td>Goal is &lt; 160 mg/dL if intermediate risk</td>
</tr>
<tr>
<td>Goal is &lt; 130 mg/dL if high risk</td>
</tr>
<tr>
<td>Consider omega-3 fatty acid supplement</td>
</tr>
<tr>
<td>HDL-C Long acting niacin, with concern for risk of inc in glucose intolerance</td>
</tr>
<tr>
<td>D Diabetes Prevention First line: Intensive lifestyle modification for all</td>
</tr>
<tr>
<td>Second line pharmacotherapy: Metformin, consider pioglitazone</td>
</tr>
<tr>
<td>Diet Weight loss</td>
</tr>
<tr>
<td>Mediterranean diet: increase omega-3 fatty acids, fruits, vegetables, fiber, nuts</td>
</tr>
<tr>
<td>Low glycemic load</td>
</tr>
<tr>
<td>E Exercise</td>
</tr>
<tr>
<td>Daily moderate to vigorous activity</td>
</tr>
<tr>
<td>Recommend use of pedometer with goal of &gt; 10,000 steps/day</td>
</tr>
</tbody>
</table>

Counseling for Lifestyle Change
Lifestyle change strategies—including setting reasonable goals, raising awareness, confronting barriers to change, managing stress, cognitive restructuring, preventing relapse, and providing support—are the keys to long-term success in managing the Metabolic Syndrome. [208]

The Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults developed by the North American Association for the Study of Obesity in conjunction with the National Heart, Lung, and Blood Institute suggests that the clinical consultation involve: [209]
"Patient-centered counseling," -- encourage patient to set goals and express their own ideas for therapy, with input from the healthcare professional.

A treatment plan that takes into account the patient's readiness for therapy and the patient's ability to comply with the plan.

Realistic goals established; frequent follow-up visits scheduled to monitor progress; modify the treatment plan as needed, and provide encouragement.

Effective therapy requires a long-term structured approach with continued support from the physician and other caregivers, particularly during periods of patient recidivism.

Attitude is important

- Patients at high risk for metabolic syndrome were stratified into attitude-behavior categories of 'Already Doing It', 'I Know I Should' and 'Don't Bother Me' and over half (54%) were in the 'Don't Bother Me' group. These are more difficult to treat with lifestyle modification approaches. [210]

Type of interventions

- A number of behavior modification strategies have shown good efficacy. These strategies include: a tailored problem-solving intervention, involving goal-setting, self-monitoring, stimulus control, cognitive restructuring, stress management, relapse prevention, social support, and contracting. [211]

- Frequent self-monitoring is especially important for continued success.

The counseling process:

- The process begins after the physician has diagnosed and explained the syndrome, discussed the associated risks and explained the treatment options, especially the need for lifestyle modification.

- It is usually carried out by a nurse or allied health professional trained in motivational interviewing and "coaching."

- Goal setting with action planning is a useful technique for engaging patients in the process. Some evidence suggests that it is effective in improving healthy behaviors, especially eating behaviors. [212]

- The American Diabetes Association, the American Association of Diabetes Educators, and the American Heart Association all recommend goal setting for cardiovascular disease risk reduction.

It is a collaborative process -- patients choose a behavior-change goal. To initiate a discussion about goal setting, ask:

- "Is there anything you would like to do this week to improve your health?"

- This question allows patients to choose a behavior they are motivated to change and forms the basis for setting a behavior-change goal. [213]

After a patient has agreed on a general goal, the patient and caregivers negotiate a specific action plan to assist in goal attainment. [214,215]

- General goals occur over a longer period of time; short-term goals can be used to identify steps toward the general goal; action plans focus on achieving specific short-term goals.

- Patients should have a high level of confidence that they can carry out their action plan; success increases self-efficacy (a person's confidence that he or she can make positive life changes).

- Ask patients to estimate, on a 0-10 scale, how confident they are that they can carry out their action plan. Action plans can be adjusted so that patients have a confidence level of at least 7 on the 10-point scale that they can succeed. Action plans can be agreed on orally or using a written form, as shown

Specific goals lead to higher performance than either no goal or vague goals.

- Specific short-term goals are associated with better performance than long-term and general goals.

- Increased self-efficacy results in people setting and achieving goals, whereas reduced self-efficacy—from failing to achieve a goal—may lead to goal abandonment. [216]

- In health-related behavior change, self-efficacy is also associated with healthier behaviors. [217]

Many studies find that regular and sustained follow-up is a necessary component of this method. Follow-up can be conducted by telephone, by e-mail, through Internet-based interactive programs, individually, or
in groups. Follow-up includes problem solving related to barriers to success in carrying out action plans. [218]

- Lack of success is translated into "lessons learned" instead of failure.
- A great advantage to doing action planning in groups, as occurs in the well-established Chronic Disease Self-Management Program, is that patients can "buddy up" and do follow-up and problem solving with each other by telephone. [219]

A training program for behavior change counseling, using goal setting and action planning has been described. [220]

10. PRACTICE REORGANIZATION – USING THE CHRONIC CARE MODEL

The management of a chronic condition, like the Metabolic Syndrome, requires a partnership between the healthcare team and the patient living with the chronic condition.

- It is something that most practices and reimbursement systems are not set up to provide.
- And, it is perhaps the greatest challenge confronting primary care physicians. [221-224]

The Chronic Care Model [225] recognizes the changes needed to organize health services for people with chronic conditions, and offers a guide for improving practice performance. The model has been endorsed by the AAFP, along with health care organizations all over the world. [226]

- It emphasizes office redesign and the use of nonphysician staff to accomplish disease management tasks. [227-230]
- The goal of the model is the development of prepared, proactive teams that prepare and partner with informed, activated patients.
- Due to time constraints, physicians have no choice but to create teams, either within the practice or using community resources, along with well written educational materials to help patients modify certain behaviors.

The model focuses on improving performance in six interrelated components: [226,231]

1) Self management support – the key to effective chronic care
   - To assist patients in becoming better informed and activated self managers
   - Includes providing encouragement and information, teaching specific skills, promoting healthy behaviors, teaching problem solving skills, assisting with emotional support, maintaining regular and sustained follow-up

2) Practice re-design – two elements required to provide self management support:
   - Planned visits – using a pre-determined agenda; can include individual or group visits, phone calls or emails, internet programs
   - Care teams – identify roles, provide needed training; includes clinicians, nurses, dietitians, social workers, behavioral health professionals, health coaches, exercise therapists, community health workers

3) Decision support -- using evidence-based recommendations and guidelines
   - Chart reminders for recommended services and
   - Electronic record protocols for referrals to specialists

4) Clinical Information Systems – to track care
   - Develop registry – patient list with preventive and chronic care needs and relevant clinical information
   - Team member designated to periodically review, update, identify needed services, reminders to send out
   - Separate registries can be created for patients with the Metabolic Syndrome, or other chronic conditions, or other specific criteria

5) Health care organization – two key elements required to redesign the practice:
   - Leadership – understand and embrace the Chronic Care Model
   - Financing – comprehensive per-patient payments rather than fee for service financing, which usually does not reimburse axillary services
Community Resources

• Primary care practices can rarely provide all of the services needed for patients with chronic conditions – need to know and encompass local resources to fill the gaps in promoting healthy lifestyles

A practical way to pay for and target chronic care activities is to reimburse physicians for units of service delivered by their team. California’s well-established Comprehensive Perinatal Services Program (CPSP) is a good example of a payment mechanism that supports health education and case management services through payments to physician employers. [232,233]

  o The Future of Family Medicine report predicted that implementation of the Chronic Care Model would have a positive impact on office costs after making assumptions regarding time required and reimbursement for providing high-quality care. [234]

The AMA Roadmap for Clinical Practice for the Assessment and Management of Adult Obesity is very helpful also for managing the Metabolic Syndrome. It contains 10 booklets of which numbers 4 (Dietary management), 5 (Physical activity management) and 9 (Setting up the office environment) are particularly useful. [See Resources]

11. THE BOTTOM LINE

Questions have been raised about the scientific basis of the metabolic syndrome, but this is a research issue; the controversy in no way negates the value of using the syndrome to describe a common phenotype of patients encountered in clinical practice that have a very high risk for developing diabetes and CVD.

  o There is no ambiguity that physicians should aggressively treat the entire cardiovascular risk factor profile concurrently in individuals with metabolic syndrome. [235]

There is also some confusion about the use of the MS to predict cardiovascular events.

  o The dichotomous nature of diagnosis, the lack of age, LDL cholesterol, family history and smoking are part of this. [236]
  
  o As such it is not meant to be a substitute for, but rather an addition to, standard cardiovascular risk assessments. As Yusuf says in a CME program about the syndrome, “it is a useful construct because it gets us to think about multiple risk factors”. [237]
  
  o And, the syndrome is better at predicting the development of Type 2 diabetes. This alone gives it a very important role in clinical practice.

Most importantly, with the Metabolic Syndrome, is doing something about it.

  o Whether the underlying cause is insulin resistance, inflammation or simply environmental changes, the best treatment is increasing physical activity and changing eating habits.
  
  o As Haffner says, “one of the important things potentially is that the metabolic syndrome encourages providers to look for other risk factors, and in particular it encourages behavioral therapy rather than just treating the risk factors individually with pharmacologic therapy.” [238]
  
  o Clinicians know what patients need to do, but getting them to do it is a different matter.
  
  o If it was easy to help patients lose fat and become more active, obesity and the metabolic syndrome, Type 2 diabetes and cardiovascular disease, would not all be epidemics.
  
  o Fortunately, clinical strategies are evolving on both the lifestyle and the pharmaceutical sides of the treatment paradigm.
    ▪ Behavior change strategies are becoming more systematic, and the keys to success at the different motivational stages are being developed, and
    ▪ New drugs that will treat the underlying insulin resistance and obesity are on the horizon for those who need them.
12. RESOURCES

GUIDELINES:

Diagnosis and Management of the Metabolic Syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement: Executive Summary
- http://circ.ahajournals.org/cgi/content/full/112/17/e285

- Table 10A. ATP III: The Metabolic Syndrome
- Table 10B. Lifestyle Risk Factors for Metabolic Syndrome and Therapeutic Recommendations
- Table 10C. Metabolic Risk Factors for Metabolic Syndrome and Therapeutic Recommendations


- Includes the minimum physical activity recommendations for managing chronic conditions and enhancing health in adults 18-65

- Guideline to effective approaches to behavioral dietary counseling in primary care
- Includes the 5-A behavioral counseling framework and office level system changes to support counseling

Treatment of the Metabolic Syndrome – Finnish Medical Society, 2007
- A guideline for treating the Metabolic Syndrome (MS) including both lifestyle and drug therapy

Preventing cancer, cardiovascular disease, and diabetes. A common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association.
- Available from the AHA website: http://circ.ahajournals.org/cgi/content/full/109/25/3244

Screening for metabolic syndrome in adults -- University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program
- Provides detailed step by step guidelines for dietary and nonpharmacologic treatment of metabolic syndrome; broken down by visits for first four visits

University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program. Screening for metabolic syndrome in adults. Austin (TX): University of Texas at Austin, School of Nursing; 2004 May. 24 p

CONSENSUS STATEMENTS:
Lipoprotein Management in Patients with Cardiometabolic Risk. Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation Diabetes Care 31:811-822, 2008 http://care.diabetesjournals.org/cgi/content/full/31/4/811

MEASURING WAIST CIRCUMFERENCE:
A short video showing how to take the measurement http://media.metabolicsyndromeinstitute.com/fichiers-site-mets/waist_circumference.mpg

CARDIOVASCULAR RISK ASSESSMENT TOOLS:
Framingham Risk Assessment Tool
- Estimates 10-year risk for “hard” coronary heart disease outcomes (myocardial infarction and coronary death)

PROCAM Risk Calculator
- Estimates risk of a heart attack within the next 10 years based upon data of the PROCAM Study

OFFICE SYSTEMS AND PRACTICE ORGANIZATION:
Roadmap for Clinical Practice series: Assessment and Management of Adult Obesity:
- This is a key resource for enhancing any aspect of obesity management. It consists of 10 booklets that offer practical recommendations for the primary care setting.
  Booklet 1 - Introduction and clinical considerations
  Booklet 2 - Evaluating your patients for overweight or obesity
  Booklet 3 - Assessing readiness and making treatment decisions
  Booklet 4 - Dietary management
  Booklet 5 - Physical activity management
  Booklet 6 - Pharmacological management
  Booklet 7 - Surgical management
  Booklet 8 - Communication and counseling strategies
  Booklet 9 - Setting up the office environment
  Booklet 10 - Resources for physicians and patients
http://www.ama-assn.org/ama/pub/category/10931.html

ORGANIZATIONS:
The Metabolic Syndrome Institute
- Created in 2003, an independent and nonprofit association; members are international experts in lipid metabolism, diabetes, heart disease, endocrinology obesity, genetics, epidemiology, basic research and health economics.
- First association totally devoted to the dissemination of knowledge about the metabolic syndrome.
http://metabolic-syndrome-institute.com/

American Heart Association
- Resources for Healthcare Professionals
http://www.americanheart.org/presenter.jhtml?identifier=3052043
ON-LINE PRESENTATIONS
Powerpoint presentation on the Metabolic Syndrome

CME PROGRAMS:
Fighting the Clinical "Battle of the Bulge"

Obesity, Insulin Resistance, and Atherosclerosis: Can the Cycle Be Broken?

Cardiometabolic Risk Reduction in Patients With Type 2 Diabetes: Evolving Science and Emerging Strategies

Targeting the Interplay of Obesity, Insulin Resistance and Mixed Dyslipidemia: An Integrative Approach to Reducing Cardiometabolic Risk

PATIENT INFO
- What is the Metabolic Syndrome? Available at:
  http://www.nhlbi.nih.gov/health/dci/Diseases/ms/ms_whatis.html
- Who is at risk for the Metabolic Syndrome? Available at:
- Active at Any Size. Available from WIN and online at
- Do You Know the Health Risks of Being Overweight? Available from WIN and online at
- Healthy Eating and Physical Activity Across Your Lifespan: Better Health and You (Tips for Adults). Available in English and Spanish. Available from WIN and online at
- Just Enough for You: About Food Portions. Available from WIN and online at
- Weight Loss for Life. Available from WIN and online at
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