Acknowledgements

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Purpose

The purpose of this course is to provide the healthcare professional with an overview of metabolic disease, so that they can educate the public in the prevention of this disease, as well as cardiovascular disease, stroke, and diabetes.
Learning Objectives

After successful completion of this course, you will be able to:
1. Identify five major risk factors for metabolic syndrome.
2. Explain the role of leptin in metabolic syndrome.
3. Discuss insulin resistance.
4. Identify four causative factors in the pathophysiology of metabolic syndrome.
5. Describe the process for diagnosing metabolic syndrome.
6. Outline management strategies for metabolic syndrome.
7. Examine two ways to prevent metabolic syndrome.

Introduction

Metabolic syndrome is a constellation of insidious pathological processes that significantly increase the risk for heart disease, diabetes, cancer, stroke, and dementia (Lydon, 2009). The term “metabolic” refers to the biochemical processes involved in the body’s normal functioning.

First identified in the 1980s, metabolic syndrome was previously known by other names, such as:
- Syndrome X
- Pre-diabetes
- Dysmetabolic syndrome
- Hypertriglyceridemic waist
- Obesity syndrome
- Insulin resistance syndrome

Metabolic syndrome is characterized by the presence of several specific risk factors for coronary heart disease in one person. In general, a person with metabolic syndrome is twice as likely to develop heart disease and five times as likely to develop diabetes as someone without metabolic syndrome.

In addition to increased risk for cardiovascular disease and diabetes, people with metabolic syndrome are also more likely to develop other conditions, such as polycystic ovary syndrome in women, certain types of liver disease, gallstones, asthma, sleep problems, and some cancers (NHLBI, 2010).

Overall, metabolic syndrome increases the risk of early death to about the same degree as cigarette smoking (AHA, 2010).
Test Yourself

Metabolic syndrome is a major health concern today because:
   A. It is a very difficult disease to treat.
   B. More obese people will require hospitalization.
   C. The risk of developing other diseases is increased.
   D. The management of this disease increases healthcare costs.

The correct answer is C.

Statistics

Approximately 47 million adults in the United States (almost 25%) have metabolic syndrome, and the numbers continue to grow (AHA, 2010). The incidence of metabolic syndrome is equal in men and women. However, African American and Mexican American women are more likely to have metabolic syndrome than their male counterparts.

The increasing number of people with this condition is connected to the rise in obesity rates among adults. In the future, metabolic syndrome may overtake smoking as the leading risk factor for heart disease.

In adults 60 years of age and older, about 45% have metabolic syndrome. Pediatricians report that children as young as seven years of age are developing metabolic syndrome, a condition once seen only in adults (AHA, 2010).

Some racial and ethnic groups in the United States are at higher risk for metabolic syndrome than others:
   • Mexican Americans have the highest rate of metabolic syndrome, 32%
   • Caucasians 24%
   • African Americans have lower rates, 22%

(AHA, 2010)
Test Yourself

Children are also at risk for developing metabolic syndrome.
   A. True
   B. False

The correct answer is true.

Risk Factors

The U.S. National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) established five features for the diagnosis of metabolic syndrome. A person can develop any one of these risk factors by itself, but they tend to occur simultaneously:

   I. Abdominal obesity (large waistline)
   II. High triglyceride levels
   III. Low HDL cholesterol levels
   IV. Hypertension
   V. Hyperglycemia/insulin resistance

The more risk factors an individual has, the greater the chance of developing heart disease, diabetes, or a stroke.
Risk Factors

Risk Factor I:
Abdominal obesity (large waistline): Equal to or greater than 35” for women and equal to or greater than 40” for men.

Excess fat in the abdominal area is a greater risk factor for heart disease than excess fat in other parts of the body, such as on the hips, buttocks, or thighs.

Many experts believe the “obesity epidemic” is mainly responsible for the increasing number of people with the metabolic syndrome in the United States; two out of three American adults are considered overweight or obese.

However, abdominal obesity, identified by an increased waist measurement, is a better predictor of metabolic syndrome than body weight alone. Too much abdominal fat is believed to trigger the release of several harmful substances into the bloodstream. Although abdominal obesity is a key feature of the metabolic syndrome, some individuals can have metabolic syndrome with lesser degrees of or non-abdominal obesity. Some men develop metabolic syndrome when their waist measurement is only slightly increased, for example, 37-39 inches (94-102 cm).

Risk Factor II:
High triglyceride levels equal to or greater than 150 mg/dL.

Risk Factor III:
Low HDL (high density lipoprotein) cholesterol levels less than 50 mg/dL for women and less than 40 mg/dL for men.

HDL is considered “good” cholesterol because it lowers the risk of cardiovascular disease. Low levels of HDL increase the risk.

Risk Factor IV:
Hypertension occurs when blood pressure is equal to or higher than 130/85 mmHg.

If either the systolic or the diastolic pressures are increased, the risk factor for metabolic syndrome is present.
Risk Factors

Risk Factor V:
Hyperglycemia/insulin resistance occurs when a fasting blood sugar equal to or greater than 100 mg/dL.

A normal blood sugar is less than 100 mg/dL. Fasting blood sugar between 100 and 125 mg/dL is considered pre-diabetes (NHLBI, 2010). Fasting blood sugar of 126 mg/dL or higher is considered diabetes. The American Diabetes Association (ADA, 2009) has recently established a cut point of 100 mg/dl (or 5.6 mmol/L), at or above which a person has an elevated fasting blood glucose level.

According to a recent National Heart, Lung, and Blood Institute (NHLBI)/American Heart Association (AHA) conference, this new cut point should be used for identifying people with the metabolic syndrome.

Test Yourself

According to the ADA, an elevated fasting blood sugar level is more than:

A. 80 mg/dl
B. 90 mg/dl
C. 100 mg/dl
D. 110 mg/dl

The correct answer is C.
Additional Risk Factors

Other groups that are at increased risk of developing metabolic syndrome include:
- People with a sibling or parent with diabetes
- Women with a personal history of polycystic ovarian syndrome (a tendency to develop cysts on the ovaries)

Genetics (ethnicity and family history) and age are other important underlying causes of metabolic syndrome. However, these risk factors cannot be modified.

Pathophysiology of Insulin Resistance

Dietary sugars and starches are changed into glucose for cellular energy. The hormone insulin, produced by the pancreas, then moves the glucose out of the blood and into the cells.

Insulin resistance is present in the majority of people with metabolic syndrome. This occurs when the body does not respond to insulin as well as it should and resists taking glucose into the cells. This can then cause hyperglycemia to develop.

High blood glucose levels are harmful and can damage organs in the body. Moreover, insulin resistance forces the pancreas to produce extra insulin in order to move glucose into cells. High levels of insulin in the blood also has harmful effects on the body, including the increased storage of fat in the abdomen.
Glucose Intolerance

People with insulin resistance often go on to develop type II diabetes. However, many years before developing type II diabetes people with insulin resistance often have impaired fasting glucose (also called glucose intolerance or pre-diabetes). People with impaired fasting glucose have fasting blood glucose levels that are higher than normal but not high enough to be diagnosed as diabetes.

The American Diabetes Association has recently changed its definition of impaired fasting glucose from values ranging from 110-125 mg/dl (or 6.1-7.0 mmol/L) to values ranging from 100-125 mg/dl (or 5.6-7.0 mmol/L).

Insulin Resistance and Metabolic Syndrome

Insulin resistance generally, but not always, rises with increases in body fat. Many of the other features of the metabolic syndrome may be linked to insulin resistance. In fact, some experts believe that insulin resistance directly causes all of the features of metabolic syndrome (ADA, 2010).

Researchers don’t know all of the exact causes of insulin resistance. Too much body fat, particularly abdominal obesity, and lack of physical activity have been shown to promote the development of insulin resistance. Another contributing factor is heredity.

People with impaired fasting glucose have pre-diabetes because many of them will eventually develop type II diabetes. People with impaired fasting glucose should take special care to maintain normal body weight, lead a physically active lifestyle, and watch for the symptoms of diabetes.
Diabetes and Metabolic Syndrome

People with diabetes should be aware that it is possible to have diabetes and also have metabolic syndrome. People with diabetes who also have metabolic syndrome are at greater risk for complications than people with diabetes who don’t have metabolic syndrome. People with diabetes and the metabolic syndrome should be especially sure to lead a healthy lifestyle and take the other necessary steps to manage their diabetes and various features of metabolic syndrome.

Other major risk factors for the development of metabolic syndrome include the presence of:

- A prothrombotic state (high fibrinogen or plasminogen activator inhibitor in the blood).
- A pro-inflammatory state (elevated C-reactive protein in the blood).

(AHA, 2010)

Test Yourself

Insulin resistance is inversely proportional to body mass.

A. True
B. False

The correct answer is false.
Causative Factors

Metabolic syndrome has several causes that act together. Some can be controlled or modified, while others cannot.

Causes that can be controlled include excess weight and obesity, lack of physical activity, and insulin resistance.

Lack of sufficient exercise is a potential underlying cause of all of the five features of metabolic syndrome:

1. Abdominal obesity
2. High triglycerides
3. Low HDL ("good") cholesterol
4. High blood pressure
5. High fasting blood glucose

Approximately 70% of U.S. adults can be classified as being sedentary (AHA, 2010).

Uncontrollable factors include age and genetics.
Additional Causative Factors

Two other conditions are often found in people with metabolic syndrome, although it’s not known if they cause it or worsen it. The two conditions are:

1. A tendency to form blood clots (coagulation disorder)
2. A tendency to have a constant, low-grade inflammation throughout the body

Additional conditions that are being studied to see whether they have links to metabolic syndrome include:

- Fatty liver (excess triglycerides and other fats in the liver)
- Polycystic ovarian syndrome (a tendency to develop cysts on the ovaries)
- Gallstones
- Breathing problems during sleep such as sleep apnea

Good risk factor management can help prevent people with metabolic syndrome from developing coronary heart disease, type II diabetes, and other health problems. The greatest potential for prevention and treatment of the syndrome lies in reversing its root causes – overweight/obesity and physical inactivity.

The Link Between Metabolic Syndrome and Stroke

Mounting evidence points to an association between metabolic syndrome and first or recurrent stroke.

Recent data has emerged that supports a link between stroke and metabolic syndrome.

These research findings underscore the need to better understand the pathophysiology of metabolic syndrome, so that the multiple risk factors associated with this disease can be modified, and the risk of stroke and cardiovascular disease limited (Nursing & Allied Health Connection, 2008).
The Link Between Metabolic Syndrome and Heart Disease

Having metabolic syndrome increases the risk for heart disease.

Heart disease risk can be divided into short-term risk (the risk for having a heart attack or dying of heart disease in the next ten years) and long-term risk (the risk for developing heart disease over a lifetime).

Major Risk Factors for Heart Disease
The major risk factors for heart disease include:

- Increased LDL cholesterol (low-density lipoprotein cholesterol) and total cholesterol levels
- Cigarette smoking
- Hypertension equal to or greater than 140/90 mmHg (or long term antihypertensive therapy)
- Decreased HDL cholesterol (high-density lipoprotein cholesterol) level equal to or less than 40 mg/dL
- Age: Men 45 years and older; women 55 years and older
- Family history of early heart disease or sudden death (in a father or brother before the age of 55, or in a mother or sister before the age of 65)
Heart Disease Risk Categories

The National Cholesterol Education Program (NCEP) divides short-term heart disease risk into four categories:

<table>
<thead>
<tr>
<th>Heart Disease Risk Category</th>
<th>Presence of Risk Factors</th>
<th>Ten Year Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk category</td>
<td>Presence of heart disease or diabetes</td>
<td>More than 20%</td>
</tr>
<tr>
<td>Moderately high risk category</td>
<td>Presence of two or more risk factors</td>
<td>0-20%</td>
</tr>
<tr>
<td>Moderate risk category</td>
<td>Presence of two or more risk factors for heart disease</td>
<td>Less than 10%</td>
</tr>
<tr>
<td>Lower risk category</td>
<td>Zero to one risk factor for heart disease</td>
<td>Low risk score</td>
</tr>
</tbody>
</table>

Ten Year Risk

These risk factors are used to calculate the ten year risk of developing heart disease. The NCEP has an [online calculator](#) that can be used to determine the ten year heart disease risk score.

Even if the ten year risk score isn’t high, over time metabolic syndrome will increase the risk for heart disease. This means that, regardless of the short-term risk category, metabolic syndrome should be treated (mainly with lifestyle changes).

**Every person with metabolic syndrome should have his or her ten year risk score calculated.**
Understanding Leptin

Abdominal obesity is a hallmark characteristic of metabolic syndrome. Until very recently, there appeared little most people could do to significantly reduce excess abdominal fat.

One of the most frustrating problems middle-aged people encounter is an increase in belly fat that is resistant to most diet and exercise programs. Abdominal weight gain is not only cosmetically unsightly, but sets the stage for a host of degenerative diseases.

In fact, a new study showed that even in people who are not considered overweight, excess belly fat of as little as two inches increased the risk of death in men by 17% and women by 13%. (Lydon, 2009).

We now know that a phenomenon called leptin resistance plays a major role in the development of abdominal obesity.

What is Leptin?

Leptin is a hormone, produced by adipocytes (fat cells), that functions to maintain a lean body composition by at least two distinct mechanisms:

First, it modulates appetite by binding to the hypothalamus, where it signals satiety. Normally, a well-nourished state is reflected by an increase in leptin levels which signal the hypothalamus to limit hunger.

Second, leptin enhances the body's ability to access and utilize fat stores as an energy source (Wang, 2005).
Leptin Resistance
Although leptin acts to maintain a lean body composition, leptin resistance can occur in obese individuals.

Since being overweight leads to chronically elevated levels of the hormone leptin, scientists hypothesize that prolonged exposure to high leptin levels in the blood can eventually cause target tissues to become immune to the effects of leptin, losing the normal capacity to respond to it (Hamann & Matthaei, 1996).

Investigators are still hard at work figuring out the exact interplay between genes and hormones. Nevertheless, many aspects of leptin resistance have already been successfully deciphered and described in the scientific literature.

Acquired Leptin Resistance
Studies have conclusively demonstrated that both the total amount of body fat, as well as the size of the individual fat cells, correlate directly to the amount of leptin an individual produces (Halaas et al, 1995). In other words, the fatter the individual, the greater the amount of leptin available in the bloodstream.

Similar to insulin resistance, an acquired leptin resistance can develop. Research has shown that overweight individuals have far more serum leptin than their normal weight counterparts.
How Leptin Affects Overall Health

Being chronically overweight leads to chronically elevated leptin levels, and chronically elevated leptin eventually causes target tissues, namely adipocytes (fat cells) and neurons, to lose the capacity to respond to it.

As the size and number of adipocytes increase with weight gain, they pump more and more leptin into the circulation in an attempt to send the message to the brain that fat stores are adequate, and food intake needs to be curbed. However, because these same fat cells are constantly bathed in elevated levels of leptin, they progressively lose sensitivity to the hormone.

Inadequate Receptor Sensitivity

This inadequate receptor sensitivity translates into diminished responsiveness, which has unfortunate results:

- Normal fatty acid oxidation (fat burning) within the adipocyte significantly declines.
- Adipocytes become less inclined to absorb free fatty acids from the circulation. The resulting excess of fatty acids floating in the bloodstream causes a functional insulin resistance in peripheral tissues like muscle.

(Kraegen & Cooney, 2008)

Test Yourself

Low levels of circulating leptin are linked to metabolic syndrome.

A. True  
B. False

The correct answer is false.
Escalating Leptin Resistance

As with leptin-resistant fat cells, insulin-resistant muscle cells lose their responsiveness, in this case, to insulin. As a result, glucose molecules are blocked from entering muscle tissue, causing blood sugar to rise. The liver senses hyperglycemia and responds by breaking down the sugar molecules and transforming them into more free fatty acids. In turn, these additional free fatty acids contribute to increased fat stores, increased leptin production, escalating leptin resistance, and the vicious cycle continues to snowball (Martin, et al., 2008).

The Affect of Leptin on Neurons

Unfortunately, adipocytes are not the only cells that submit to the effects of chronically elevated leptin. Once leptin resistance begins to take hold, neurons in the hypothalamus also show decreased responsiveness to circulating leptin.

However, these same neurons respond normally to leptin if it is injected directly into the brain, suggesting that, unlike adipocytes, neurons retain their leptin receptors despite leptin resistance (Harris, 2000).
Preventing Leptin Resistance

Healthy lifestyle choices can prevent systemic inflammation and all its negative consequences, including leptin resistance.

Well-established means by which one can thwart the onset of chronic inflammation and maintain a healthy body weight include:

- Avoiding highly processed foods
- Supplementing the diet with omega-3 essential fatty acids, and
- Engaging in regular physical activity

Leptin and Weight Loss

Unfortunately, research has shown that once an individual becomes leptin resistant, it is much more difficult to lose weight (Dagogo-Jack, 1996).

Since most overweight individuals do suffer from some degree of leptin resistance, it is not surprising that weight loss has become a multi-billion dollar industry in the US today.

In addition, about 90% of people who have successfully lost weight in the past will gain those pounds back within a year.

Now, thanks to emerging studies on leptin resistance, researchers are beginning to realize that weight reduction itself may launch yet another vicious cycle that makes it exceedingly difficult to maintain leanness.
**Fluctuations in Leptin Levels**

Leptin production correlates to adiposity; it rises or falls naturally with increasing or diminishing body fat, respectively. However, if weight gain is substantial or protracted enough to provoke the development of leptin resistance, subsequent weight loss appears to cause a state of "relative leptin insufficiency" (Lydon, 2009).

In essence, after you've been overweight, the amount of leptin your body requires to stay lean may exceed what your "thin self" (and correspondingly shrunken fat stores) can produce. Once relative leptin insufficiency rears its ugly head, adaptations to muscle metabolism and modulations in sympathetic and autonomic hormones function make weight regain all but inevitable.

Investigations have tried to override relative leptin insufficiency with exogenous leptin with limited success. A recent study using recombinant human leptin did not improve insulin action in obese patients with type 2 diabetes (Mittendorfer, 2011).

Like other hormones, leptin's effects throughout the body are far-reaching and complex; it may be years before we have a satisfactory grasp of the health repercussions of casual leptin use.

Already, current research suggests that elevated leptin provokes the growth of certain malignancies, including many forms of breast cancer (which helps explain the higher breast cancer risk observed in overweight women).

**Chronically high serum leptin is believed to increase stroke risk and promote cardiac hypertrophy.**

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**Test Yourself**

Leptin production rises as body fat decreases.

A. True  
B. False

The correct answer is false.
C-Reactive Protein

C-reactive protein (CRP) is a class of proteins in human blood that interact directly with serum leptin, and is a marker of systemic inflammation and a predictor of cardiac risk.

Recent studies have shown that elevated CRP levels double a patient's chances of dying within the first 28 days following acute myocardial infarction (Kuch, 2008).

CRP is produced by adipocytes and liver cells, and binds to leptin. In binding to leptin, CRP inhibits the negative feedback mechanism of leptin, and satiety (feeling full) is not recognized.

By blocking leptin's physiological functions, CRP represents a powerful component in the progression of leptin resistance and escalating weight gain.

Signs and Symptoms of Metabolic Syndrome

Metabolic syndrome is made up of a group of factors that can increase risk even if they are only moderately raised (borderline-high risk factors).

Most of the risk factors linked to metabolic syndrome have no obvious external sign, although a large waistline is a visible indicator of risk.

Some people may have symptoms of high blood sugar (if diabetes is present) or, occasionally, hypertension. Symptoms of hyperglycemia often include:

- Increased thirst
- Frequent urination, especially at night
- Fatigue and blurred vision

Hypertension is initially asymptomatic, but may present with dull headaches, dizzy spells, or frequent nosebleeds.

Metabolic syndrome itself usually has no symptoms.
Diagnosis of Metabolic Syndrome

There is no well-accepted criteria for diagnosing metabolic syndrome, but most doctors use the criteria proposed by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (AHA, 2010).

According to the ATP III criteria, metabolic syndrome is identified by the presence of three or more of these risk factors:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity as measured by waist circumference</td>
<td>Men: Greater than 40 inches</td>
</tr>
<tr>
<td></td>
<td>Women: Greater than 35 inches</td>
</tr>
<tr>
<td>Fasting blood triglycerides</td>
<td>Greater than or equal to 150 mg/dL</td>
</tr>
<tr>
<td>Blood HDL cholesterol</td>
<td>Men: Less than 40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Women: Less than 50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Greater than or equal to 130/85 mm/Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Greater than or equal to 100 mg/dL</td>
</tr>
</tbody>
</table>

The ATP III panel did not find evidence to recommend routine measurement of insulin resistance (e.g., increased fasting blood insulin), prothrombotic state or proinflammatory state.

**No single test can identify metabolic syndrome.**

**To diagnose metabolic syndrome, there must be at least three out of five identified risk factors present.**
Management of Metabolic Syndrome

More studies are needed to understand the relationship between risk factors for metabolic syndrome and the efficacy of drug therapy in people who have metabolic syndrome (AHA, 2010).

In addition to lifestyle interventions, steps for managing metabolic syndrome that are important for patients and their doctors include:

- Routinely monitor body weight (especially the index for central obesity), blood glucose, lipoproteins, and blood pressure.
- Treat individual risk factors (hyperlipidemia, hypertension and high blood glucose) according to established guidelines.
- Carefully select anti-hypertensive drugs because different agents have different effects on insulin sensitivity.

Healthy Lifestyle Changes

Healthy lifestyle changes are the first line of treatment for metabolic syndrome.

Lifestyle changes include weight loss, increased physical activity, improved diet, and smoking cessation.
Specific Treatment Modalities: Nonpharmacological

Specific treatment modalities revolve around lifestyle management strategies that promote healthier lifestyles, in terms of nutrition, exercise, smoking cessation, and stress management.

In general, people with metabolic syndrome who are overweight or obese are urged to reduce their weight by 7-10% during the first year of treatment. For example, a person weighing 250 pounds should try to lose 18-25 pounds. A person weighing 300 pounds should try to lose 21-30 pounds (NHLBI, 2010).

Determining Healthy Weight

In addition to body weight, there are two other ways to determine healthy weight:

1. Waist measurement
2. Body mass index (BMI)

A waist measurement indicates the amount of abdominal fat and is linked to the risk for cardiac disease.

BMI measures your weight in relation to your height and provides an estimate of your total body fat. A BMI between 25 and 29.9 is considered overweight. A BMI of 30 or more is considered obese. A BMI of less than 25 is the goal for preventing metabolic syndrome, and it’s also the goal when treating metabolic syndrome (NBHLI, 2010).

Overweight individuals are urged to lose weight slowly and steadily, with a long-range target of lowering the body mass index (BMI) to less than 25.

To minimize the risk of developing metabolic syndrome, body mass index (BMI) should be less than 25.

You can calculate your BMI using the National Heart, Lung, and Blood Institute’s (NHLBI’s) online calculator: http://www.nhlbisupport.com/bmi/
Specific Treatment Modalities: Nutrition

The NHLBI offers a Therapeutic Lifestyle Changes (TLC) diet. With this diet, less than 7% of daily calories come from saturated fat, and no more than 25-35% of daily calories should come from all fats, including saturated, trans, monounsaturated, and polyunsaturated fats. The diet limits cholesterol intake to less than 200 mg a day of cholesterol. The amounts of fat and cholesterol in prepared foods can be found on the food’s nutritional label.

Foods high in soluble fiber are also part of a healthy eating plan. These foods include:

- Whole grain cereals such as oatmeal and oat bran
- Fruits such as apples, bananas, oranges, pears, and prunes
- Legumes such as kidney beans, lentils, chick peas, black-eyed peas, and lima beans

Fish are an important part of a heart healthy diet. Fish are a good source of omega-3 fatty acids, which may help protect the heart from blood clots and inflammation and reduce the risk for heart disease.

The amount of sodium and salt should also be limited. This means choosing low-sodium and low-salt foods and “no added salt” foods and seasonings at the table or when cooking.

Alcoholic beverages are also limited. Alcohol increases blood pressure and triglyceride levels. It also adds extra calories. Men should have no more than two drinks containing alcohol a day. Women should have no more than one alcoholic drink per day (AHA, 2010).

Specific Treatment Modalities: Physical Activity

In general, people with metabolic syndrome are urged to keep up a moderate level of activity, such as brisk walking for at least 30 minutes at least five days of the week. This activity can be broken into shorter periods as needed; for example, three ten minute sessions.

The ultimate goal is for people to maintain a moderate level of physical activity 60 minutes a day for 5 days a week, but preferably daily.
Specific Treatment Modalities: Smoking Cessation

Smoking raises triglyceride levels and lowers HDL cholesterol, as well as causing additional cardiovascular changes.

Clients should be counseled on quitting smoking and referrals made to appropriate support groups.

Pharmacological Management: Overview

Pharmacological management is the next line of treatment. Medications are used to treat and control individual risk factors such as high blood pressure, high triglycerides, low HDL cholesterol (high-density lipoprotein cholesterol), and high blood sugar.

- Cholesterol-lowering agents include statins, fibrates, and nicotinic acid.
- Antihypertensives include diuretics and angiotensin-converting enzyme (ACE) inhibitors.
- Hyperglycemia is managed with oral antiglycemic agents, such as metformin, insulin injections, or both.
- Low-dosage daily aspirin therapy can help reduce the risk of forming blood clots, especially for people at high risk for heart disease.

Daily aspirin also may be used prophylactically to reduce the risk of blood clots.
Cholesterol Management

It is important for patients with metabolic syndrome to continue lifestyle modification, as discussed previously, even when medication is prescribed for cholesterol management.

Total blood cholesterol is composed of subunits called lipoproteins. Low density lipoprotein (LDL) is the atherogenic subunit and is often the main target for lipid lowering therapy.

Cholesterol Management Goals

The usual goal for LDL is <100-140mg/dL, or even as low as <70 for high risk patients. High-density lipoprotein (HDL) is the beneficial subunit. Increased levels of HDL have been shown to correlate with coronary heart disease (CHD) reduction. The usual goal for HDL in men is >40mg/dL and >50mg/dL in women. A high triglyceride level is also considered an independent risk for CHD and should be lowered to <150mg/dL in most patients. LDL particles contribute to the development of fatty deposits in the arteries and HDL helps to remove excess LDL from the blood.
Drug Therapy for Hypercholesterolemia

Several drug therapy options are available to treat hypercholesterolemia. The HMG-Co-A inhibitors, or statins, are generally considered first-line therapy in most patients. Examples include simvastatin and atorvastatin among several others. Statins inhibit the hepatic enzyme responsible for cholesterol synthesis, up-regulating LDL receptor activity to reduce circulating LDL.

While these drugs are well tolerated, some patients may develop myalgia, myopathy and increased liver enzymes. Patients should promptly report any unexplained muscle pain and/or weakness, or dark-colored urine while taking a statin. These drugs are Category X for use in pregnancy. Maximum doses of these drugs can yield up to a 40-60% decrease in LDL when used with lifestyle modifications. The statins produce greater dose-related decreases in LDL, relative to other drug classes.

Fibric acid derivatives, or fibrates, include gemfibrozil and fenofibrate. These drugs increase hepatic fatty acid metabolism and decrease secretion of triglyceride-containing lipoproteins. They are primarily used to treat isolated hypertriglyceridemia.

Niacin is a useful drug to treat mixed hypercholesterolemia. This drug reduces liver synthesis of triglycerides and inhibits the mobilization of free fatty acids. Side effects may include flushing, hyperglycemia, hyperuricemia, dyspepsia and rarely hepatotoxicity. Niacin decreases LDL and triglycerides, but raises HDL levels. The incidence of headache and flushing can be decreased by titrating the dosage up slowly, using a sustained-release preparation, and pre-treating with a prostaglandin inhibitor, such as aspirin or ibuprofen.

Bile acid sequestrants, such as cholestyramine bind bile acids in the intestine, interrupting their enterohepatic circulation and increasing hepatic conversion of cholesterol into bile acids. These drugs cause gastrointestinal complaints, such as constipation, flatulence and bloating.

Ezetimibe is a drug that acts at the brush border of the small intestine and inhibits cholesterol absorption. This results in a decrease in the delivery of intestinal cholesterol to the liver, which decreases hepatic cholesterol stores and increases clearance of cholesterol from circulation. Ezetimibe can be used as an alternative to statins or niacin if patients develop intolerable side effects.
## Cholesterol and Triglyceride Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>Side Effects &amp; Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pravachol (pravastatin)</td>
<td>1. Daily (evening)</td>
<td>• Muscle pain</td>
</tr>
<tr>
<td>2. Zocor (simvastatin)</td>
<td>2. Daily (evening)</td>
<td>• Liver functions tests should be performed periodically</td>
</tr>
<tr>
<td>3. Mevacor (lovastatin)</td>
<td>3. Once or twice daily</td>
<td></td>
</tr>
<tr>
<td>4. Lipitor (atorvastatin)</td>
<td>4. Once or twice daily</td>
<td></td>
</tr>
<tr>
<td>5. Lescol (fluvastatin)</td>
<td>5. Daily (evening)</td>
<td></td>
</tr>
<tr>
<td>6. Crestor (rosuvastatin)</td>
<td>6. Daily</td>
<td></td>
</tr>
<tr>
<td><strong>Resins/Bile Acid Binding Drugs</strong></td>
<td>BID within an hour of major meals</td>
<td>• Upper and lower gastrointestinal discomfort</td>
</tr>
<tr>
<td>1. Questran Powder</td>
<td></td>
<td>• Triglycerides may increase</td>
</tr>
<tr>
<td>(cholestyramine)</td>
<td></td>
<td>• With the exception of WelChol, these drugs interfere with adsorption of other drugs</td>
</tr>
<tr>
<td>2. Questran Lite</td>
<td></td>
<td>• Administer all other medications at least one hour before or three hours after these drugs</td>
</tr>
<tr>
<td>(cholestyramine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Flavored Colestid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(colestipol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Colestid Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(colestipol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. WelChol (colesevelam)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Cholesterol Absorption Inhibitors</strong></td>
<td>1. Once daily</td>
<td>• Gastrointestinal discomfort</td>
</tr>
<tr>
<td>1. Zetia (ezetimibe)</td>
<td>2. 3-4 times daily</td>
<td>• Liver function tests should be performed periodically when taken together with a statin and/or due to risk for liver inflammation (hepatitis)</td>
</tr>
<tr>
<td>2. Niacin (nicotinic acid)</td>
<td>3. Daily or BID</td>
<td>• Common side effects include flushing and itching</td>
</tr>
<tr>
<td>3. Cholestyramine (questran)</td>
<td>4. Daily or BID</td>
<td>• Blood glucose and uric acid may increase; these values should be monitored periodically</td>
</tr>
<tr>
<td>4. Niaspan (extended-release niacin)</td>
<td>5. Daily or BID</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Lopid (gemfibrozil)</td>
<td>1. BID: 30 minutes before morning and evening meals</td>
<td>• Abdominal discomfort</td>
</tr>
<tr>
<td>2. Tricor (fenofibrate)</td>
<td>2. Daily, with meal</td>
<td>• Diarrhea or nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver function tests should be performed periodically</td>
</tr>
</tbody>
</table>
Hypertension Management

It is important for patients with hypertension to continue lifestyle modification, as discussed previously, even when medication is prescribed. The classes of medications used to treat hypertension include angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor antagonists (ARB), direct renin antagonists, calcium channel blockers (CCB), alpha-1 blockers, direct vasodilators, diuretics, beta blockers (BB), potassium-sparing diuretics, aldosterone receptor blockers, and centrally acting, alpha-2 antagonists.

<table>
<thead>
<tr>
<th>Classes of Medications Used to Treat Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting-enzyme inhibitors (ACEI)</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists (ARB)</td>
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<tr>
<td>Direct renin antagonists</td>
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<tr>
<td>Calcium channel blockers (CCB)</td>
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<tr>
<td>Alpha-1 blockers</td>
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<tr>
<td>Direct vasodilators</td>
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<tr>
<td>Diuretics</td>
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<tr>
<td>Beta blockers (BB)</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
</tr>
<tr>
<td>Aldosterone receptor blockers</td>
</tr>
<tr>
<td>Centrally acting, alpha-2 antagonists</td>
</tr>
</tbody>
</table>

The most common combination type drugs for reducing hypertension are ACEI's and CCB's, ACEI's and diuretics, ARB's and diuretics, BB's and diuretics, and centrally acting drugs and diuretics. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) provides guidelines for management of hypertension, including which drugs are preferred in certain patient types. Health professionals can review these guidelines at [http://www.nhlbi.nih.gov/guidelines/hypertension](http://www.nhlbi.nih.gov/guidelines/hypertension).

**Note!**

- A thiazide diuretic has traditionally been considered the first-line antihypertensive in the absence of compelling indications that would favor a different agent (Bui, 2010). Blood pressure should be lowered to <130/80 mmHg in those with diabetes.
Managing Hypertension and Diabetes

Since most patients with metabolic syndrome have hyperglycemia, initial treatment with an ACEI or ARB is preferred; however, many patients will require combinations of antihypertensive drugs for optimal control.

The decision of which drug to add is complex and depends on numerous factors, such as, other underlying disease states, patient preference and tolerability, as well as cost.

Note!

- Not all patients with metabolic syndrome develop diabetes, but those who do should receive either an ACEI, or an ARB.

Based on human data, both classes for drugs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs and ARBs should be discontinued once pregnancy is confirmed.

Side Effects of ACE Inhibitors

Patients should be made aware of symptoms before initiating treatment. Symptoms include lip and tongue swelling, difficulty breathing, and edema around the larynx.

Angioedema is the rapid swelling (edema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues. It is a rare (<1%) but serious side effect of ACE Inhibitors. It can occur at any time during treatment, but most often after the first dose.

Another potential side effect of ACE Inhibitors is a persistent dry and unproductive cough. It usually develops during the first few months of treatment, and is much less likely to develop with an ARB.
Test Yourself

The most serious side effect of ACE inhibitors is:

A. Myalgia  
B. Angiodema  
C. Hepatotoxicity  
D. None of the above

The correct answer is B.

Managing Hyperglycemia

A detailed discussion of managing hyperglycemia and type 2 diabetes is beyond the scope of this educational module. Patients with metabolic syndrome, often, but not always, have glucose intolerance. Some will meet criteria for diabetes, and should be managed with a combination of medical nutrition therapy, exercise, lifestyle modification, and possibly drug therapy.
Managing Hyperglycemia: Metformin

Drugs that improve glucose tolerance, do not adversely affect lipids, and do not cause weight gain should be used initially. The prototype drug with all three characteristics is metformin. Metformin plus lifestyle intervention is usually started initially, and then maximized.

Numerous additional medication options are available. The choice of add-on therapy is complex, and each drug class has its benefits and liabilities. Please see the table below for a comparison of mechanisms, dosing, side effects, warnings, and clinical notes.

Managing Hyperglycemia: Insulin Therapy

Some patients will eventually require insulin therapy since oral agents, even when given in combination in an adherent patient, may fail to provide adequate glycemic control. A discussion of various insulin products is outside the scope of this educational module.
Managing Hyperglycemia: Alpha-Glucosidase Inhibitor (AGI)

A1C-Lowering Effect/Mechanism of Action:
• 0.5-0.8%
• Competitive inhibitor of alpha-amylase (pancreas) and alpha-glucosidase (intestinal brush border)
• Results in delayed glucose absorption
• Reduces postprandial serum insulin and glucose peaks

Specific Agents/Dose:
Acarbose (Precose®)
• Initial dose: 25mg TID
• Maintenance: 50-100mg TID
• Max: 300mg/day
Miglitol (Glyset®)
• Initial: 25mg TID
• Maintenance: 50mg TID
• Max: 300mg/day

Common Adverse Effects:
• Gas
• Bloating
• Diarrhea

Contraindications/Warnings/Precautions:
• Contraindicated in patients with chronic intestinal disorders
• May intensify hypoglycemic effects of other anti-diabetic medications
• Not recommended for use in patients with SCr >2mg/dL

Place in Therapy/Clinical Pearls:
• Weight neutral
• Consider for use in patients with elevated postprandial glucose
• Should be taken with the first bite of each meal
• Dose may be titrated upwards after 4-8 weeks
• Side effects should diminish over time
Managing Hyperglycemia: Amylin Analog

A1C-Lowering Effect/Mechanism of Action:
- 1-2%
- Prolongs gastric emptying time
- Reduces postprandial glucagon secretion
- Reduces caloric intake by suppressing appetite

Specific Agents/Dose:
Pramlintide (Symlin®)
- Initial dose: 60mcg SC before major meals
- Maintenance dose: 120mcg SC before major meals

Common Adverse Effects:
- Hypoglycemia
- Nausea
- Vomiting
- Anorexia
- Headache

Contraindications/Warnings/Precautions:
- U.S. Boxed Warning co-administration with insulin may cause severe hypoglycemia
- Reduce insulin dose by 50% when starting pramlintide
- Do not use in patients with A1C >9% or recurrent hypoglycemia
- Contraindicated in patients with gastroparesis or hypoglycemia unawareness

Place in Therapy/Clinical Pearls:
- Weight loss
- Can be used as an adjunct to prandial insulin to decrease postprandial glucose
- Should only be given with meals >250 kcal or >30 g carbohydrate
- Titrate dose upwards after 3-7 days
- Remain at 60mcg dose if patient experiences intolerable nausea at 120 mcg dose
- Inject into thigh or abdomen, not arm due to variable absorption
Managing Hyperglycemia: Biguanide

A1C-Lowering Effect/Mechanism of Action:
- 1-2%
- Improves insulin sensitivity to increase glucose uptake and utilization
- Inhibits hepatic production of glucose
- Reduces intestinal glucose absorption

Specific Agents/Dose:
*Metformin* (Glucophage®, Glucophage XR®)
Immediate-Release:
- Initial dose: 500mg QD-BID, 850mg QD
- Maintenance dose: Up to 2000mg/day
  - given BID
  - Max dose: 2550mg/day

Extended-Release:
- Initial dose: 500mg QD
- Max dose: 2000mg QD

Common Adverse Effects:
- Diarrhea
- Nausea
- Vomiting
- Flatulence

Contraindications/Warnings/Precautions:
- U.S. Boxed Warning risk of lactic acidosis
- Contraindicated in males with SCr >1.5mg/dL and females with SCr >1.4mg/dL
- Contraindicated in those with reduced CrCl for any reason, including shock, acute myocardial infarction, septicemia, heart failure
- Contraindicated in those with acute or chronic metabolic acidosis

Place in Therapy/Clinical Pearls:
- Weight neutral/weight loss
- Considered first-line therapy
- Titrate dose upwards every 1-2 weeks to minimize gastrointestinal adverse effects
- Take with food and avoid alcohol
- Temporarily discontinue prior to/at time of iodinated contrast media use; restart 48 hours or longer after study completion
Managing Hyperglycemia: Bile Acid Sequestrant

A1C-Lowering Effect/Mechanism of Action:
- 0.5%
- May decrease insulin resistance and hepatic glucose production
- May reduce intestinal glucose absorption

Specific Agents/Dose:
Colesevelam (Welchol®)
- 3.75g QD or 1.875g BID

Common Adverse Effects:
- Constipation
- Abdominal discomfort

Contraindications/Warnings/Precautions:
- Contraindicated in patients with serum triglycerides >500mg/dL or pancreatitis associated with hypertriglyceridemia
- Use with caution in patients with serum triglycerides >300mg/dL or intestinal disease

Place in Therapy/Clinical Pearls:
- For those patients with dyslipidemias (LDL reduction of up to 20%)
- For use in combination with oral medications or insulin, not monotherapy
- Take with meals and liquid
- Take other medications one hour before or four hours after colesevelam
Managing Hyperglycemia: Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor

A1C-Lowering Effect/Mechanism of Action:
- 0.5-0.8%
- Inhibition of DPP-IV results in prolonged active incretin levels
- Incretin causes increased insulin synthesis and release and decreased glucagon secretion resulting in decreased glucose production

Specific Agents/Dose:
Linagliptin (Tradjenta®)
- 5mg QD

Saxagliptin (Onglyza®)
- 2.5-5mg QD

Sitagliptin (Januvia®)
- 100mg QD

Common Adverse Effects:
- Edema
- Headache
- Sinusitis
- Abdominal discomfort
- Diarrhea
- Hypoglycemia
- Urinary tract infection

Contraindications/Warnings/Precautions:
- Reduce dose of insulin secretagogues when used in combination
- Saxagliptin and sitagliptin require dose adjustment for renal impairment
- Saxagliptin requires dose reduction with CYP3A4 inhibitors
- Risk for pancreatitis (reports seen with sitagliptin)

Place in Therapy/Clinical Pearls:
- Weight neutral
- For use as monotherapy or in combination with other anti-diabetic agents
- For use in patients with elevated postprandial and fasting glucose
Managing Hyperglycemia: Dopamine Agonist

A1C-Lowering Effect/Mechanism of Action:
- 0.5%
- Unknown for diabetes; may play a role in circadian rhythms that play a part in obesity and insulin resistance

Specific Agents/Dose:
*Bromocriptine* (Cycloset®)
- Initial dose: 0.8mg QD
- Maintenance dose: 1.6-4.8mg/day
- Max dose: 4.8mg/day

Common Adverse Effects:
- May result in increased risk for hypoglycemic events when used with hypoglycemic agents; dose reduction in hypoglycemic agent recommended
- Drug interactions with CYP3A4 inhibitors
- Contraindicated in patients with syncopal migraines or taking dopamine agonists

Contraindications/Warnings/Precautions:
- May result in increased risk for hypoglycemic events when used with hypoglycemic agents; dose reduction in hypoglycemic agent recommended
- Drug-interactions with CYP3A4 inhibitors
- Contraindicated in patients with syncopal migraines or taking dopamine agonists

Place in Therapy/Clinical Pearls:
- Limited data for use in combination with other anti-diabetic agents
- Titrate upwards by 0.8mg at weekly intervals
- Take with food to decrease stomach upset
- Take within two hours of waking
- Do not discontinue abruptly, may result in withdrawal reaction
Managing Hyperglycemia: Glucagon-Like Peptide-1 (GLP-1) Agonist; Incretin Mimetic

A1C-Lowering Effect/Mechanism of Action:
- 0.5-1.1% (exenatide)
- 1-1.5% (liraglutide)
- Acts as incretin; results in increased insulin secretion, decreased glucagon secretion, slowed gastric emptying; decreases food intake

Specific Agents/Dose:
**Exenatide** (Byetta®)
- Initial dose: 5mcg SQ BID within 60min before a meal
- Maintenance dose: 5-10mcg SQ BID within 60min before a meal

**Liraglutide** (Victoza®)
- Initial Dose: 0.6mg SQ QD for one week
- Maintenance dose: 1.2-1.8mg SQ QD

Common Adverse Effects:
- Nausea
- Vomiting
- Diarrhea

Contraindications/Warnings/Precautions:
- Risk for pancreatitis and acute renal failure
- May result in increased risk for hypoglycemic events when used with hypoglycemic agents
- Dose reduction of hypoglycemic agent recommended
- Exenatide not recommended for use in CrCl <30
- Liraglutide U.S. Boxed Warning risk of thyroid C-cell tumor

Place in Therapy/Clinical Pearls:
- Weight loss
- For use as monotherapy or in combination with other anti-diabetic agents, including long-acting insulin
- May reduce rate and extent of absorption of oral medications due to effects on gastric emptying
- Exenatide (based on response) may increase to 10mcg BID after one month at 5mcg BID
- Liraglutide 0.6mg not therapeutic
Managing Hyperglycemia: Meglitinide

A1C-Lowering Effect/Mechanism of Action:
- 0.5-1.5%
- Stimulates release of insulin from pancreatic beta-cells (secretagogue)

Specific Agents/Dose:
Nateglinide (Starlix®)
- 120mg TID before meals

Repaglinide (Prandin®)
- Initial dose: A1C <8%: 0.5mg TID before meals; A1C >8%: 1-2mg TID before meals
- Maintenance dose: 0.5-4mg TID before meals
- Max dose: 16mg/day

Common Adverse Effects:
- Hypoglycemia
- Dizziness
- Headache
- Upper respiratory infection

Contraindications/Warnings/Precautions:
- Use with caution in elderly and malnourished patients, may be more susceptible to hypoglycemia
- Repaglinide requires dose adjustment for renal impairment; do not use with NPH insulin due to risk for myocardial ischemia

Place in Therapy/Clinical Pearls:
- Weight gain
- For use in patients with elevated postprandial glucose
- Not recommended for use as monotherapy despite indication
- If other agents stimulating insulin release are not effective, do not switch to a meglitinide
- Repaglinide more effective than nateglinide in terms of A1C-lowering effect; titrate dose upwards (double the dose) at weekly intervals based on fasting glucose
Managing Hyperglycemia: Sulfonylurea

A1C-Lowering Effect/Mechanism of Action:
- 1-2%
- Stimulates release of insulin from pancreatic beta-cells (secretagogue)

Specific Agents/Dose:
Chlorpropamide (Diabinese®)
Initial dose: 250mg QD, 100-125mg QD in elderly
Maintenance dose: 100-250mg QD
Max dose: 750mg/day

Glyburide (Diabeta®, Glynase®, Micronase®)
Initial dose: 2.5-5mg QD with first meal
Maintenance dose: 1.25-20mg/day divided QD-BID
Max dose: 20mg/day

Glipizide (Glucotrol®)
Initial dose: 5mg QD with first meal
Maintenance dose: Doses >15mg/day should be divided BID
Max dose: 40mg/day

Glimepiride (Amaryl®)
Initial dose: 1-2mg QD with first meal
Maintenance dose: 1-4mg QD
Max dose: 8mg/day

Common Adverse Effects:
- Hypoglycemia
- Dizziness
- Headache
- Nausea
- Diarrhea
Managing Hyperglycemia: Sulfonylurea

Contraindications/Warnings/Precautions:
- Use with caution in elderly and malnourished patients, may be more susceptible to hypoglycemia
- Risk of cross-reaction in those with sulfonamide allergy
- Avoid chlorpropamide in patients with renal impairment or the elderly
- Glyburide may cause more hypoglycemia than other agents; avoid use in renal impairment
- Glipizide is preferred agent in renal impairment; consider dose adjustment for renal impairment
- Glimepiride requires dose adjustment for renal impairment

Place in Therapy/Clinical Pearls:
- Weight gain
- Administer 30 minutes before meal
- Reduced efficacy over time
- Chlorpropamide is not a recommended agent, titrate dose up or downwards at 3-5 day intervals by 50-125mg/day
- Glyburide regular and micronized tablets are not interchangeable; titrate dose upwards by 2.5mg/day at weekly intervals
- Titrate Glipizide dose upwards by 2.5-5mg/day every few days
- Titrate Glimepiride dose upwards by 2mg/day at 1-2 week intervals
Managing Hyperglycemia: Thiazolidinedione (TZD)

A1C-Lowering Effect/Mechanism of Action:
- 0.5-1.4%
- Agonist at peroxisome proliferator-activated receptor-gamma
- Insulin dependent
- Improves cell response to insulin by increasing production of gene products related to glucose and lipid metabolism

Specific Agents/Dose:
**Pioglitazone** (Actos®)
- Initial dose: 15-30mg QD
- Max dose: 45mg/day

**Rosiglitazone** (Avandia®)
- Initial dose: 4mg/day divided QD or BID
- Maintenance dose: 4-8mg/day divided QD or BID

(Nathan DM, Buse JB, Davidson MB, et al., 2009)

Common Adverse Effects:
- Edema (most common when taken in combination with insulin or sulfonylurea)
- Upper respiratory tract infection
- Heart failure
- Headache

Contraindications/Warnings/Precautions:
- U.S. Boxed Warning: May cause or exacerbate heart failure; contraindicated in patients with NYHA Class III or IV heart failure
- When used in combination with sulfonylurea, sulfonylurea dose may need to be reduced if hypoglycemia reported
- Do not initiate during active liver disease; discontinue if patient becomes jaundice or LFTs remain elevated
- Increased risk of fractures in females (lower limb or distal upper limb)
- Pioglitazone when used in combination with insulin, insulin dose should be reduced by 10-25%; increased risk for bladder cancer, especially in those receiving higher doses and/or longest exposure; do not use in those with active bladder cancer or those with a prior history
- Rosiglitazone to avoid concomitant use with insulin; has increased risk of cardiovascular events, including myocardial infarction and stroke
Managing Hyperglycemia: Thiazolidinedione (TZD)

Place in Therapy/Clinical Pearls:
- Weight gain
- For use as monotherapy or in combination with other anti-diabetic agents
- Consider for use in patients with metabolic syndrome and nonalcoholic fatty liver disease; may improve lipid profile
- Pioglitazone may improve lipid profile
- Titrate Rosiglitazone dose upwards after 8-12 weeks if needed
- Rosiglitazone restricted access and distribution; only those who are currently benefiting from the medication, those who cannot obtain glycemic control with other anti-diabetic agents, or those who are not willing to use pioglitazone are able to receive medication; only available from specialty pharmacies

Aspirin Therapy

Since most patients with metabolic syndrome by definition have some combination of central obesity, hypertension, dyslipidemia and glucose intolerance, many are at increased risk for thrombotic events. The routine use of daily aspirin and other anticoagulants for secondary prevention of stroke or other forms of thrombosis is a widely accepted practice. However, the choice of daily aspirin use for primary prevention of cardiovascular events depends on a multitude of factors.

For primary prevention of cardiovascular disease, the American College of Chest Physicians suggest low-dose aspirin (75-100 mg/d) in patients aged >50 years, and use in all patients with established coronary artery disease with dosing based on underlying disease and/or cardiovascular procedure (Vandvick, 2012).
**Goals of Treatment**

The major goal of treating metabolic syndrome is to reduce a person’s risk for heart disease. Treatment is directed first at reducing LDL cholesterol (low-density lipoprotein cholesterol), high blood pressure, and diabetes (if these conditions are present).

The second goal of treatment is to prevent the onset of type II diabetes, or management of the condition, if it exists. Long-term complications of diabetes often include heart and kidney disease, vision loss, and foot or leg amputation. If diabetes is present, the goal of treatment is to reduce the increased risk for heart disease by controlling all of the risk factors.

**The main emphasis in the treatment of metabolic syndrome is to lessen the effects of the underlying risk factors that can be controlled, such as being overweight, lack of physical activity, and an unhealthy diet.**

---

**Prevention of Metabolic Syndrome**

The cornerstone of prevention and treatment of the metabolic syndrome is lifestyle management. The safest and most effective way to improve all of the risk factors for the metabolic syndrome is by eating healthy, losing weight, and increasing physical activity.

An integrated approach to lifestyle management has been shown to be effective in preventing and treating the metabolic syndrome.

Encouraging healthy lifestyle choices is the best way to help your patient prevent metabolic syndrome. Maintaining a healthy weight is important. A healthy weight can be maintained by regular weighing.

Small but significant lifestyle changes can reduce the risk of developing metabolic syndrome. Following a sensible diet, incorporating daily exercise into routines and scheduling regular physician visits to track cholesterol, blood pressure, and blood sugar levels, will help to minimize the risk of developing metabolic syndrome.
Test Yourself

The best way to assist your patient in avoiding metabolic syndrome is by encouraging healthy lifestyle changes.
   A. True
   B. False

The correct answer is true.

Current Research

Researchers in Spain have linked a low intake of selenium with a higher risk of metabolic syndrome. They studied 100 healthy young adults and measured selenium in the participants' nails, the most accurate reflection of intake.

They also measured blood levels of complement factor 3 (C3), an indicator of inflammation; elevated levels are linked to metabolic syndrome.

They found that low levels of selenium corresponded to high levels of C3, suggesting an increased risk of metabolic syndrome (European Journal of Clinical Nutrition, November 5, 2008).
The Link Between Breast Cancer and Metabolic Syndrome

According to the results of a national study, the constellation of factors that comprise metabolic syndrome may increase the risk of postmenopausal breast cancer.

Researchers suspect that metabolic syndrome could lead to breast cancer by affecting interrelated hormones of the two conditions, such as insulin, estrogen, cytokines, and growth factors.

Other studies seeking to connect breast cancer with individual components of metabolic syndrome have had inconsistent results.

Conclusion

Metabolic syndrome is a lifelong condition. However, lifestyle changes can help reverse or reduce the risk factors for heart disease and diabetes, and it is possible to prevent or delay metabolic syndrome with these changes.

The healthcare professional plays an important role in educating the public about this disease. Knowledge of the risk factors can encourage individuals to make healthy lifestyle changes that can significantly decrease their risk of developing metabolic syndrome.

A healthy lifestyle is a lifelong commitment. Successfully controlling metabolic syndrome takes a long-term effort and teamwork.
Resources

NHLBI Resources:  http://www.nhlbi.nih.gov/health/dci/Diseases/ms/ms_all.html
Aim for a Healthy Weight:  
Heart Attack Risk Assessment Tool:  
Interactive Menu Planner:  http://hp2010.nhlbihin.net/menuplanner/menu.cgi
Overweight and Obesity (Diseases and Conditions Index):  
Portion Distortion:  http://hp2010.nhlbihin.net/portion/

Non-NHLBI Resources
Metabolic Syndrome (MedlinePlus):  

Clinical Trials
Current Research (ClinicalTrials.gov):  http://clinicaltrials.gov/
References


References


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