REX HEALTHCARE

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The Metabolic Syndrome

Introduction: The Metabolic Syndrome is defined as a cluster of cardiovascular risk factors characterized by insulin resistance and associated with the development of type 2 diabetes and cardiovascular disease. The Metabolic Syndrome is also known as syndrome X or the insulin resistance syndrome. Early identification, treatment and prevention are essential to avoid the inevitable complications. The World Health Organization and the National Cholesterol Education Program Adult Treatment Panel III (ADT III) have recently published definitions of the Metabolic Syndrome. While there are slight differences between the two they are quite similar. The ADT III definition is listed in the table below and is easily adapted to an office practice.

General features of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal Obesity (waist circumference)	
Men	> 102 cm (> 40 in.)*
Women	> 88 cm (> 35 in.)
Elevated triglycerides	≥ 150 mg/dl
Low HDL cholesterol	
Men	< 40 mg/dl
Women	< 50 mg/dl
Raised blood pressure	≥ 130/85 mm Hg.
Fasting glucose	≥ 110 mg/dl

*Some males can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g. 94-103 cm (37-39 in). Such persons may have a strong benefit from changes in life habits, especially weight reduction.

In order to qualify for the Metabolic Syndrome, one must have any 3 of 5 risk factors listed above:

- Abdominal obesity and waist circumference of greater than 102 cm or 40 inches for men and greater than 88 cm or 35 inches for women;
- Triglycerides equal to or greater than 150 mg/dl;
- HDL cholesterol under 40 mg/dl. for men and under 50 mg/dl. for women. (The ADT III guidelines define low HDL cholesterol as under 40 mg/dl, but for purposes of the Metabolic Syndrome the values are set at a different level for women.);
- Elevated blood pressure (systolic over 130 mm Hg. or a diastolic over 85 mm. Hg.); or
- Fasting glucose equal to or greater than 110 mg/dl.

The combination of a physical examination with routine laboratory tests of HDL cholesterol and fasting glucose are all that is necessary to make the diagnosis. Note the ADT III did not recommend serum insulin levels as part of the evaluation even though insulin resistance underlies the pathophysiology of the syndrome.

The factors are interrelated: The root causes of the Metabolic Syndrome are obesity, physical inactivity and genetic factors. The Metabolic Syndrome is closely associated with a generalized metabolic disorder called insulin resistance, in which tissue responsiveness to the normal action of insulin is impaired. In response to the resistance, insulin levels rise and are followed by a modest increase in fasting blood glucose levels. Some persons are genetically predisposed to insulin resistance and most of these have abdominal obesity. The relationship between the risk factors is poorly understood and appears complex. The following table contains a list of those factors that are generally accepted as being characteristic and in some way related to one another.

Interrelated factors

- Abdominal Obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance +/- glucose intolerance
- Prothrombotic state
- Proinflammatory state (elevated hs CRP)

From a population viewpoint, the increasing prevalence of the Metabolic Syndrome threatens to partially reverse the reduction in CHD risk resulting from the decline in serum LDL cholesterol over the last three decades. The Metabolic Syndrome has emerged as a coequal partner to cigarette smoking as a contributor to premature cardiovascular disease. In addition, the continued insulin resistance that accompanies the Metabolic Syndrome is one of the underlying causes of type 2 diabetes.

Pathophysiology: Diabetes has been elevated as an equivalent to cardiovascular disease in the ADT III guidelines. The prediabetic state (the Metabolic Syndrome) is also defined in an attempt to focus on treatment prior to the development of disease. Haffner and others have described the "ticking clock" hypothesis for both microvascular and macrovascular complications associated with diabetes. For microvascular complications, (primarily the eye, the kidney, and the nervous system), the clock starts ticking at the onset of hyperglycemia. But for macrovascular complications, (cardiovascular disease) the clock begins ticking even before the diagnosis of type 2 diabetes. It is believed that some of Metabolic Syndrome abnormalities actually contribute to the development of type 2 diabetes. Therefore, intervening at the early stage may actually prolong or possibly prevent the onset of overt diabetes.

"TICKING CLOCK" HYPOTHESIS

For	the "clock starts ticking"
Macrovascular Complications	Before the diagnosis of hyperglycemia
Microvascular Complications	At the onset of hyperglycemia

Treatment goals for the Metabolic Syndrome:
Aggressive early treatment is recommended. The December 4, 2002 issue of JAMA reported increased mortality in men with the Metabolic Syndrome, even in the earlier phases, before the development of cardiovascular disease and overt diabetes. The two primary goals are to prevent the development of type 2 diabetes and cardiovascular disease. The greatest potential for management of the syndrome lies in reversing its root causes.

Management of the Metabolic Syndrome

Therapeutic Lifestyle Changes

- Dietary restriction of total calories, simple carbohydrates and saturated fat
- Regular aerobic exercise
- Weight control

Pharmacologic therapy for

- Hypertension
- Glucose intolerance/diabetes
- Dyslipidemia

Pharmacologic therapy for hypertension, glucose intolerance and abnormal lipids are familiar to most physicians and will not be discussed here. On the other hand, lifestyle changes are the least expensive and perhaps the most important to change but also can be the most difficult. Remember that even modest lifestyle changes can have a major impact in decreasing risk. Dietary changes are essential; however it is not a simple issue. In contrast to lowering LDL cholesterol, where the major issue with diet is restriction of saturated fat, these patients need to drastically alter their eating habits if they are going to reverse the risks. They need to restrict simple carbohydrates because we now recognize that simple carbohydrates drive triglyceride production and exacerbate the lipid profile in these patients. But many of them also have elevated LDL cholesterol, and restriction of saturated fat is a goal as well.

So what exactly do you tell people to do? These patients are likely to benefit from referral to a dietitian who understands the issues of carbohydrates vs. fat and can go through a practical diet that will allow them to lose weight, reduce their triglycerides, and even reduce their LDL cholesterol.

A second, and an absolute cornerstone of management, is regular aerobic exercise. These patients, in general, tend to be sedentary. Encourage simply activity, such as using the stairs for a couple of flights instead of taking elevators, brisk walking 30 minutes 5 times a week and parking far enough away for a brisk walk.

Finally, weight control can be a very important adjunct to the management of this syndrome. Even if people can't lose weight, maintenance of weight is an incredibly important issue in preventing progression of type 2 diabetes and development of cardiovascular problems.

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References

1. Hanna-Maaria, Lakka, et. al. "The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-Aged Men", JAMA, 2002:288, p2709-2716.
2. Haffner, SM, et. al., "Cardiovascular risk Factors In Confirmed Pre-diabetic Individuals", JAMA,1990:203 p. 2893-2898.
3. The Metabolic Syndrome and Cardiovascular Disease: Challenges and Opportunities Faculty: Antonio M. Gotto, Jr., MD, DPhil; Jorge Plutzky, MD; Daniel J. Rader, MD , http://www.medscape.com
4. National Cholesterol Education Program, Adult Treatment Panel III, updated 11/19/02. http://www.nhlbi.nih.gov/about/ncep/

CRP and Cardiac Risk

A panel convened by the Centers for Disease Control and the American Heart Association recently issued recommendations regarding the use of highly-sensitive C-reactive protein (hsCRP) in the evaluation of cardio-vascular disease risk. [1] While their suggestions should come as no surprise to our regular readers, a summary is provided below. [2,3] At Rex, all CRP determinations are highly sensitive-CRP. [2]

- Widespread testing for CRP (as a cardiac risk marker) is inappropriate. Testing should be reserved for those with an intermediate (10-20%) risk of developing coronary artery disease in the next 10 years as determined by the Framingham risk score
- Two CRP tests (fasting or non-fasting) taken 2 weeks apart are recommended.
- A CRP < 1.0 mg/L is considered low risk. A value > 3.0 mg/L is considered high risk. Levels between 1.0 – 3.0 mg/L are considered average risk.
- Levels > 10 mg/L suggest a confounding inflammatory condition, which would obscure cardiac risk assessment. Treatment of the underlying inflammatory condition and repeat testing is recommended.
- The authors recommend CRP be reported in units of mg/L (cf. mg/dL). (Accordingly, we will switch our units **back** to mg/L, reversing an earlier decision. [2] It's easier to follow rather than lead.)

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References

1. Pearson, TA *et al*. Markers of inflammation and cardiovascular disease. *Circulation* 2003; 107:499-511.
2. Benson, JD, Johnson, J, and Patterson E. High sensitivity C-reactive protein. *REX Healthcare Laboratory Bulletin* no. 60, Sept. 2001
3. Mitka M. Panel endorses limited roles for CRP tests. *JAMA* 2003; 289:973-4.

The Day the Mumps (Test) Died

Anergy testing measures the competence of the cellular immune system. One of its primary uses has been in HIV patients in conjunction with the PPD tuberculin skin test. Because no apparent benefit to this testing has been shown, the CDC no longer recommends routine anergy testing in screening programs for TB infection among HIV-infected persons. In HIV-negative patients, anergy testing has also been found to contribute very little to decisions of whether or not to treat.

At Rex hospital, we have had two methods of anergy testing, the monilia skin test and the mumps skin test antigen (MSTA). Aventis Pharmaceuticals, the only manufacturer of the MSTA is withdrawing the product due to low demand. Our current stock will last through March and the test will be discontinued on April 1, 2003.

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References

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