

**Patients with metabolic syndrome are at risk for type 2 diabetes and cardiovascular disease. How can you help?**

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Over the past 50 years, metabolic syndrome has been studied under numerous names, such as Syndrome X, insulin resistance syndrome, and dysmetabolic syndrome. The condition is closely associated with the risk for both type 2 diabetes and cardiovascular disease.<sup>1-3</sup> (See [Metabolic syndrome's pathophysiology](#).)

When the National Cholesterol

Education Program (NCEP) revised the Adult Treatment Panel III (ATP III) guidelines in 2001, metabolic syndrome became a secondary focus for cardiovascular risk factor modification, but the only patients being treated were those with low-density lipoprotein cholesterol (LDL-C).<sup>4</sup> The addition of metabolic syndrome as a focal point for cardio-

Watch that waistline



vascular risk reduction allows many individuals to be recognized, for the first time, as being at risk for type 2 diabetes and/or cardiovascular disease. Without this step, many of these individuals would have gone unrecognized and untreated until much later in the disease's trajectory.<sup>5-7</sup>

Critical care nurses must be familiar with the components of

metabolic syndrome to recognize it in their patients and help them manage this constellation of disorders. (See **Diagnostic criteria for dysmetabolic syndrome.**)

### **Clinical presentation**

There are several definitions of metabolic syndrome; however, not all are practical for clinical screening. According to the NCEP guidelines (which is the gold standard for clinical practice in the United States), to receive a diagnosis of metabolic syndrome, an individual must possess at least three of five components:

- central obesity
- hypertriglyceridemia
- low high-density lipoprotein cholesterol (HDL-C)
- hypertension
- impaired fasting glucose.<sup>1</sup>

The American College of Endocrinology (ACE) uses similar criteria, but includes, among others, hyperinsulinemia, inflammation, and a procoagulable state in its criteria for making the diagnosis.<sup>12</sup> In the future, adding separate components from other definitions of metabolic syndrome may prove to be clinically efficacious when combined with the NCEP criteria for determining early risk for cardiovascular disease. For example, a likely candidate for addition to the NCEP's criteria for metabolic syndrome is C-reactive protein (CRP), a marker of sub-clinical inflammation closely associated with abnormal endothelial function and abnormal levels of hemostatic factors, such as plasminogen activator inhibitor-1 (PAI-1), which are difficult to measure in clinical practice.<sup>23-24</sup>

C-reactive protein concentration can be severely elevated in individuals with autoimmune dis-

eases; thus a level greater than 10 mg/liter should be repeated in a few weeks when acute inflammation has gone into remission.<sup>25</sup>

Normally, a CRP level between 3 and 10 mg/liter is strongly associated with inflammation and risk for cardiovascular events.<sup>26</sup> The prognostic value of CRP makes it an efficacious test for screening an otherwise seemingly low-risk individual.

In concurrence with other definitions of metabolic syndrome, the American Diabetes Association's (ADA) Expert Committee recently suggested lower limits for impaired fasting glucose (IFG) to 100 mg/dL instead of 110 mg/dL, in an attempt to provide a viable method for earlier identification of individuals in their disease trajectory.<sup>27</sup> The NCEP has now accepted IFG as 100 to 125 mg/dL.<sup>28</sup> The ADA recommends a fasting plasma glucose as a preferred first line screening test.<sup>29</sup>

The ADA and the U.S. Preventive Services Task Force do not recommend screening asymptomatic patients for diabetes.<sup>30</sup> The ADA clearly states that high-risk patients with multiple risk factors should be screened, and patients 45 years or older should be screened every 3 years. However, clinical suspicion should be high among at-risk populations such as minorities (including African Americans, Asians, Pacific Islanders, Hispanic Americans, and Native Americans).

While the NCEP has provided feasible guidelines for practitioner use, there has been recent criticism for not including a measure of insulin resistance in the definition of metabolic syndrome. Experts argue that the NCEP's definition of metabolic syndrome

isn't sensitive enough to detect insulin resistance in patients with normal fasting glucose levels who are already at risk by virtue of their dyslipidemia and presence of insulin resistance.<sup>31</sup> Thus, many providers have begun measuring insulin levels as a proxy for evaluation of insulin resistance, especially during glucose tolerance testing.<sup>32</sup> Nonetheless, using NCEP criteria for metabolic syndrome may underestimate risk in certain populations, such as African Americans, who are frequently insulin resistant, but don't have severe hypertriglyceridemia and commonly manifest higher HDL-C levels.<sup>33</sup>

### Treatment

NCEP ATP III treatment categories identify LDL-C as the primary objective for lowering the risk of cardiac events, treating metabolic syndrome as a secondary intervention.<sup>4</sup> Lifestyle modifications are the mainstay of first-line therapy. Determining a patient's optimal cut point for LDL-C depends on his or her coronary heart disease (CHD) risk category. It's plausible that after 3 months of intensive lifestyle alterations (such as low-fat diet, increased physical activity, and intensified weight loss management), the LDL-C level may still be above the recommended cut point, in which case statins should be considered.

### CHD risk

There are three CHD risk categories, based on the NCEP ATP III strategies, which guide treatment for managing LDL-C:

1. CHD risk equivalent
2. individuals with two or more major CHD risk factors

## Metabolic syndrome's pathophysiology

Central obesity is the hallmark feature of metabolic syndrome.<sup>8</sup> Other components of the syndrome tend to group around central obesity.<sup>9-11</sup> Hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), hypertension, dysfibrinolysis (such as elevated plasminogen activator inhibitor-1 [PAI-1], fibrinogen), inflammation (such as elevated C-reactive protein), and/or elevated fasting insulin have all been associated repeatedly in individuals with an enlarged waist circumference, having met the criteria for central obesity even at normal levels of body mass index (BMI). (See **Diagnostic criteria for dysmetabolic syndrome.**)<sup>1,7,12</sup>

The deep visceral abdominal adipocytes or fat cells excrete deleterious metabolic substrates such as angiotensinogen and PAI-1, fostering a milieu for hypertension, inflammation, and dysfibrinolysis, or a procoagulable state.<sup>2,7,13,14</sup> While increased levels of plasma PAI-1 are found in individuals with hypertriglyceridemia and/or hyperinsulinemia, both substances stimulate the deep visceral abdominal adipocytes to excrete excessive plasma levels of PAI-1.<sup>15,16</sup> The deep visceral abdominal adipocytes are considered metabolically active, extremely lipolytic, and are easily broken down into free fatty acids (FFA).<sup>17</sup> The FFA may flood the liver, causing insulin resistance.

The "Portal Theory" offers some insight into the likely pathological processes that occur when metabolic syndrome is present.<sup>18</sup> The theory suggests that due to the proximity between the deep visceral abdominal adipocytes and the portal veins, the adipose tissue is broken down into FFA as these substrates barrage the liver and insulin resistance develops.<sup>19-22</sup> Therefore, centrally obese individuals commonly present with components of metabolic syndrome, including insulin resistance.

3. individuals with less than two major CHD risk factors.<sup>4</sup>

In the highest level of CHD risk categories are those patients who have CHD or one of the following:

- diabetes mellitus
- peripheral arterial disease
- abdominal aortic aneurysm
- carotid artery disease.

These patients are considered to have a CHD risk equivalent, which occurs when an individual's risk is equal to that of a patient who has already developed CHD.<sup>4</sup> This group of patients should receive the most aggressive therapy and need lipid-lowering pharmacologic interventions to meet optimal LDL-C level

guidelines. For the CHD risk equivalent group, the goal of therapy is to reduce the LDL-C to less than 70 mg/dL. Patients with a CHD risk equivalent who manifest a LDL-C level of greater than 130 mg/dL will need both aggressive lifestyle management and pharmacologic lipid-lowering intervention. When LDL-C levels are between 100 and 129 mg/dL, treatment may begin with lifestyle modification.

The second CHD risk category consists of individuals with two or more major risk factors who haven't had a coronary event and don't possess any of the CHD equivalents. These individuals need to have an LDL-C of less

than 130 mg/dL.<sup>4</sup> Although aggressive lifestyle modification is the first line of recommended therapy for these individuals, it's likely they won't reach their treatment goals. Therefore, their lipid-lowering drug therapy often begins before or by the end of 3 months of lifestyle modification. Once the LDL-C goal has been reached in this risk category, take care to address the patient's other major CHD risk factors.

The third CHD risk category consists of those individuals with less than two major CHD risk factors.<sup>4</sup> In most cases, these individuals are the most receptive to aggressive lifestyle therapies and the LDL-C treatment goal is less than 160 mg/dL. Once the LDL-C level has reached 190 mg/dL or more, and 3 months of

aggressive lifestyle has failed, lipid-lowering pharmacologic interventions are then considered cost-effective.

**Secondary focus**

As stated earlier, metabolic syndrome is now a secondary focus for cardiovascular risk modification after LDL-C treatment has begun. Watch for patients who have components of the syndrome, which are as follows:

**1. Central obesity:** Determining waist circumference with a simple tape measure can be an enlightening finding. An individual who possesses a normal body mass index and was previously judged to be at low risk for cardiovascular disease may possess considerable risk when screened for metabolic syndrome and

found to be centrally obese.<sup>9,11</sup> There are gender-specific cut points for determining central obesity. For men, waist circumference optimally should be less than 40 inches (102 cm); for women, less than 35 inches (88 cm).<sup>2</sup> Aggressive lifestyle alterations are a must for managing central obesity and the potential sequelae of metabolic syndrome. (See **Hazardous waist.**)

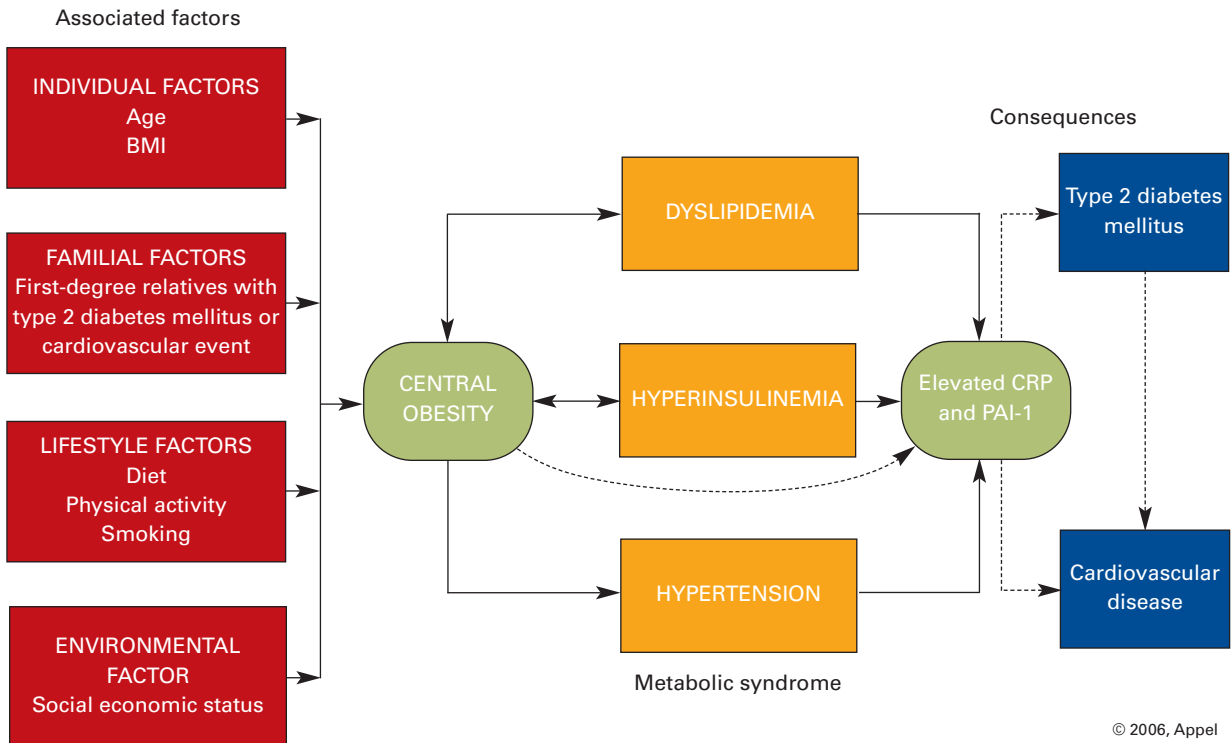
**2. Dyslipidemia (hypertriglyceridemia and low HDL-C):**

Once the LDL-C goal is attained, the next focus is to lower triglyceride levels and raise HDL-C levels. Individuals who have reached their LDL-C goal, but have triglyceride levels equal to or greater than 200 mg/dL, need to maximize lifestyle modifications and may benefit from triglyceride lowering agents (fenofibrates such as Tricor or niacin).<sup>4</sup> The optimal goal for all patients is a triglyceride level equal to or less than 150 mg/dL.<sup>4</sup> Individuals with hypertriglyceridemia often have other cardiovascular risk factors associated with metabolic syndrome (such as central obesity, hypertension, IFG or impaired glucose tolerance (IGT), hyperinsulinemia or insulin resistance, and a low HDL-C).<sup>6</sup>

Likewise, increased HDL-C levels may occur with lifestyle modifications such as weight loss, increased physical activity, and moderate alcohol consumption.<sup>34</sup> However, when the LDL-C and triglyceride levels are brought into appropriate ranges, the HDL-C may rise.<sup>25</sup> Specific agents that help lower triglycerides, such as fenofibrates or omega-3 fatty acids, may serve to raise HDL-C levels.<sup>36</sup> The NCEP has gender-

| <b>Diagnostic criteria for dysmetabolic syndrome</b>  |  |                    |
|---|--|--------------------|
| *Three or more of the following indicate dysmetabolic syndrome based on NCEP ATP II CPT-9 code 277.7. |  |                    |
| <b>Risk</b>   | <b>Results</b>   | <b>CPT-9 codes</b> |
| Central obesity   | Waist circumference<br>Men > 102 cm (> 40 in)<br>Women > 88 cm (> 35 in)       |                    |
| Dyslipidemia<br>hypertriglyceridemia*   | Triglycerides ≥ 150 mg/dL  | 272.1              |
| Low HDL-C*  | HDL-C<br>Men < 40 mg/dL<br>Women < 50 mg/dL                                    |                    |
| Hypertension*   | BP ≥ 130/85 mm Hg  | 401.9              |
| Glucose metabolism disorders  |  |                    |
| Impaired fasting glucose*   | FBS ≥ 100 and ≤ 125 mg/dL  |                    |
| Impaired glucose tolerance  | 2-hr postprandial<br>≥ 140 and ≤ 199 mg/dL                                     |                    |
| Type 2 diabetes mellitus  | FBS ≥ 126 mg/dL<br>Random glucose ≥ 140 mg/dL<br>2-hr postprandial ≥ 200 mg/dL | 250.0              |

## Hazardous waist: Factors and consequences of central obesity



specific cut points for HDL-C. For men, the optimal level for HDL-C is equal to or greater than 40 mg/dL; in women it's 50 mg/dL.<sup>4</sup>

**3. Hypertension:** The etiology of hypertension isn't fully understood within metabolic syndrome. The abdominal adipocytes excrete angiotensinogen, offering a partial explanation as to the role of hypertension within metabolic syndrome.<sup>37</sup>

Furthermore, angiotensinogen stimulates the abdominal adipocytes to produce increased plasma levels of PAI-1 and contribute to dysfibrinolysis.<sup>38</sup> These findings explain why angiotensin converting enzyme (ACE) inhibitors improve the fibrolytic profile of metabolic syndrome by reducing plasma PAI-1 levels.<sup>14</sup> Consequently, the first line of

antihypertensive management in metabolic syndrome should consist of ACE inhibitors, especially for individuals with any degree of abnormalities in glucose homeostasis or those that manifest frank type 2 diabetes.

### 4. Hyperinsulinemia and impaired fasting glucose:

Similar to hypertriglyceridemia, hyperinsulinemia is a direct effect of the abdominal adipocytes producing elevated plasma levels of PAI-1.<sup>1</sup> Early in metabolic syndrome, glucose levels may be normal, but hyperinsulinemia or insulin resistance will commonly develop over time. Initially, the fasting plasma glucose levels are within normal limits, so the individual is often erroneously considered at low risk for diabetes or cardiovascular-

related ailments. However, close examination for the other metabolic syndrome components may identify a previously classified low-risk individual as at-risk. Early intervention opportunities are present when insulin levels are elevated in association with the other components of metabolic syndrome, regardless of whether glucose levels are within normal ranges.

Individuals with either a normal fasting glucose or IFG in association with other components of metabolic syndrome should undergo an oral 75-gram glucola glucose challenge test to determine the presence of either IGT or type 2 diabetes.<sup>12</sup> It's also recommended that nurses screen for all the components of metabolic syndrome along with obtain-

ing a fasting insulin level. Several studies have shown the benefit of treating either IFG or IGT with oral antidiabetic agents such as metformin (Glucophage), prior to the development of frank type 2 diabetes.<sup>39</sup> Experts have found that although increased physical activity had the best outcome when treating IGT individuals, using metformin alone reduced

ureas will generally lower blood sugar rapidly and may also place individuals at risk for hypoglycemia. When choosing an antidiabetic agent for an overweight or obese patient, first consider metformin and one of the other drug categories before the sulfonylureas.

Keep in mind that rosiglitazone, as well as the other thiazolidine-

ty often have polycystic ovarian syndrome (PCOS)—a form of metabolic syndrome. At an earlier age, these women are at great risk for the development of type 2 diabetes, accelerated cardiovascular disease, and cardiac events.<sup>41</sup>

Often, these patients respond well to oral contraceptives and most of the antidiabetic agents, such as insulin sensitizers; consequently, they develop a more favorable metabolic profile as a result of weight loss.<sup>42</sup> An overriding concern for many of these women is that they may become pregnant, as thiazolidinediones and metformin are known for causing resumption of ovulation in a previously anovulatory women.<sup>43</sup> In these cases, the patient may have given up on ever becoming pregnant, forgoing contraception, and may not view this time in her life as appropriate. Careful reproductive counseling is mandatory in treating insulin resistance in PCOS patients.

Two notable clinical manifestations that may demonstrate risk for metabolic syndrome or type 2 diabetes are changes in skin tone and the presence of skin tags, especially when associated with central obesity. This change in skin tone, known as acanthosis nigricans (AN), can be related to hyperinsulinemia, especially among individuals of either gender who have darker skin tones.<sup>44</sup> Primarily found on the back of the neck, AN is commonly associated with a velvety thickening and darkening of the skin in areas of skin folds and can be found in the axillae, groin, or back of the neck.<sup>45</sup> The mechanism responsible for AN is the elevated insulin level, which stimulates the receptors of the

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the onset of type 2 diabetes by 58%.<sup>39</sup>

When aggressive lifestyle alterations are difficult to maintain, metformin may help to correct abnormal glucose levels. The drug also works to manage obese individuals with abnormal glucose homeostasis, as it may actually encourage weight loss. Metformin is available in combination with other helpful agents that may serve to have favorable effects on both glucose and lipids (such as lowering triglyceride levels and raising HDL-C). Another efficacious pharmacologic agent is Avandamet, a combination of rosiglitazone and metformin. Other commonly used combined medications are Glucovance (a combination of glyburide plus metformin) or Metaglip (a combination of glipizide plus metformin). Because individuals with type 2 diabetes are usually obese, the sulfonylureas may be problematic because they tend to facilitate weight gain. Sulfonyl-

diones, can cause fluid retention so use it with caution in patients who have heart failure. Metformin is contraindicated in patients with heart failure requiring pharmacologic interventions and in patients with renal dysfunction, cardiovascular collapse, myocardial infarction, hypoxia, or septicemia. Also, metformin must be held at the time of the procedure and for 48 hours subsequent to the procedure in patients having radiologic studies involving the use of contrast media.

### **Associated findings**

When a female patient has an android-like appearance, acne, oily hair, male vertex balding, alopecia, or hirsutism, she may be at risk for, or more likely already has, metabolic syndrome.<sup>40</sup> Direct interview questions toward the patient's menstrual and reproductive history. Women who experienced early menarche, irregular menses during childbearing years, or infertili-

keratinocytes and fibroblast to produce augmentation of the skin cells that become hyperplastic.<sup>45</sup> Another skin proliferation seen in insulin resistance is cutaneous papillomas (skin tags) found in the same areas as AN.<sup>40</sup>

These subtle abnormalities can alert nurses to ask more questions to determine an individual's risk for cardiovascular disease. It's important to remember that individuals in the early stages of carbohydrate disequilibrium may manifest nonspecific symptoms.

### Managing patients

Once nurses identify patients at risk, the next step is an oral glucose challenge test. Obtaining blood samples, blood pressure, or body composition measurements for all components of metabolic syndrome (such as insulin, lipids, glucose, CRP, blood pressure, and waist circumference), will provide the most detailed analysis of the patient's risk status.<sup>46</sup> Abnormal findings within this battery of tests will help determine what risk factors need to be treated or modified.

Lifestyle modifications are at the forefront of therapy. Low-density lipoprotein cholesterol levels should be optimized first, along with blood pressure, and then the specific component of metabolic syndrome. However, early introduction of pharmacologic interventions can significantly reduce risk by delaying or avoiding the development of type 2 diabetes or cardiovascular disease among individuals with metabolic syndrome. ❖

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