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The Metabolic Syndrome: An Interplay of Multiple Subtle Cardiovascular Risk Factors

Case Study and Commentary: Benjamin J. Ansell, MD

DR. LIANG:

Metabolic syndrome, also known as syndrome X, insulin resistance syndrome, plurimetabolic syndrome, and the “deadly quartet,” describes a cluster of patient risk factors comprising abdominal obesity, hypertension, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia.¹⁻⁴ Although more formally described in 1988,⁵ initial observations and clustering of risk factors have been reported as early as 1923.⁶ The syndrome itself is considered a risk factor for cardiovascular disease as well as type 2 diabetes.⁷⁻⁹

Metabolic syndrome is quite common in the United States. It is estimated that approximately 22% to 24% of the population are affected by the syndrome, which translates into roughly 47 million affected individuals using figures from the 2000 census.¹⁰ Age is clearly a factor, with a prevalence of 43.5% of those aged 60 to 69 years compared with a prevalence of only 6.7% among those aged 20 to 29 years.¹⁰

Racial and gender disparities also exist. In the United States, Mexican Americans have the highest prevalence of the metabolic syndrome, whereas white persons have the lowest. Mexican American women have a 26% higher prevalence than Mexican American men, and the gender disparity is even greater in African Americans, with African American women having an astounding 57% higher incidence of the syndrome than African American men.¹⁰ In addition, women with gestational diabetes have a higher risk of developing the syndrome.¹¹ Underscoring the importance of this entity, patients with metabolic syndrome are at heightened risk for increased mortality from all causes.¹²

The intersecting clinical and laboratory findings have made the etiology of the syndrome unclear. Insulin resistance appears to be a fundamental feature of the metabolic syndrome.¹³ Genetic abnormalities, fetal malnutrition, and visceral adiposity all may play some role in the syndrome's pathophysiology and the insulin resistance characteristic of it.¹⁴ However, some patients

do not exhibit insulin resistance.¹⁵ In addition, there have been reports of subclinical atherosclerosis in patients with metabolic syndrome, but the specific relationship between this finding and other aspects of the syndrome is unclear.¹⁶ Factor analysis has been performed, and has suggested that at least 2 pathophysiologic processes are involved in the syndrome, which may account for the varying presentations and morbidities associated with it.¹⁷

It is important to note that significant policy issues require addressing with regard to metabolic syndrome. At present, key factors in treatment of the disease, as noted in this case study, include education, weight training, and therapeutic lifestyle changes.¹⁰ However, provider and patient reimbursement occur rarely for at least the first 2 of these activities. This is particularly disconcerting when recent research suggests that lower levels of education and socioeconomic status are associated with an increased risk for metabolic syndrome.^{11,18} Thus, the most effective interventions of this quite common condition, with its attendant morbidity and mortality, are not encouraged by the financial policies of public and private payers. Such a state of affairs requires addressing to integrate important treatment methodologies and to provide appropriate incentives to engage in these effective and relevant modalities.

A similar policy issue arises with regard to the characteristics of the syndrome itself. Particularly in the elderly, the presence of 1 risk factor should spur the primary care physician to investigate the potential for other factors that might point toward the presence of metabolic syndrome in a patient. Owing to steadily

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decreasing funds available for health care, particularly in the Medicare and Medicaid programs and under managed care budgets, there may be an incentive to simply treat a single aspect of the disease, rather than understand and address the issues associated with the syndrome as a discrete entity. This is another area in which patients with the disease may not be provided with optimal care due to financial considerations.

Overall, metabolic syndrome is a common, important entity. Primary care physicians see these patients in their daily practice. It is essential that providers assess the syndrome's factors if even a single one is present in a presenting patient. However, by engaging patients to increase their physical activity and make appropriate lifestyle changes, accompanied by judicious pharmacotherapy, these patients will be able to manage their risk factors and become empowered to have an impact upon the outcomes of their care.

DR. ANSELL:

Coronary heart disease (CHD) is the largest killer of American men and women, accounting for more than 500,000 deaths and 1.2 million myocardial infarctions each year.¹⁹ Major independent risk factors for CHD have been identified; these include diabetes mellitus, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, hypertension, smoking, family history of premature vascular disease, male sex, and advancing age.²⁰ However, many patients develop CHD in the absence of traditional risk factors. Such patients often have multiple subtle biochemical abnormalities, none of which is aberrant enough to be considered a risk factor by itself. However, several of these apparently mild pathologic markers appear to contribute to CHD risk and may coexist as part of a "metabolic syndrome." This syndrome, now formally defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP-III), is considered to be a secondary target for CHD risk reduction therapy beyond LDL lowering.²⁰

The following case involves a patient who exhibits the constellation of abnormalities commonly seen in the metabolic syndrome. This article reviews the multifaceted treatment approach that is often necessary for optimal cardiovascular risk reduction.

CASE STUDY

Initial Presentation

A 41-year-old Mexican American man presents to a new primary care physician for evaluation of chronic low back pain. He says that his wife suggested that he

also get a "complete check-up" because it has been several years since the patient was last seen by a physician.

History

The patient reports that he has been troubled by lower back pain for years, typically worse after working or prolonged periods on his feet. The pain is a bilateral aching in the lumbar region and not associated with any radicular or neuropathic symptoms. He finds that it is improved by either hot showers or anti-inflammatory agents, but he prefers not to take any medication unless he "really needs it." In recent months, the pain has worsened enough so as to limit his activities, and he has become increasingly sedentary as a result.

Prior history is remarkable for appendectomy as a youth and having being told that his blood pressure and cholesterol were "a little high" on 1 occasion. He has been overweight for most of his adult life and experienced a 10-lb weight gain in association with his reduction in physical activity in the preceding 2 to 3 months.

The patient works as a grocery clerk; he and his wife have 3 children. He smoked while in high school, but not since, and drinks 2 to 3 beers each weekend. His brother and mother both have hypertension. His mother also has type 2 diabetes. His father, who was also overweight, underwent coronary bypass surgery at age 53, later dying of a stroke.

Physical Examination

The patient is a pleasant, articulate man who is 5 ft 10 in (1.78 m) tall and weighs 237 lb (107.5 kg). His body mass index is 34 kg/m². He displays a central pattern of obesity, with a waist measurement of 42 in (107 cm). His blood pressure is 138/88 mm Hg initially and 133/86 mm Hg on repeat measurement. His heart rate is 76 bpm and regular. Funduscopic examination is unrevealing, and he has no goiter or carotid bruits. His lungs are clear, and his cardiac examination is within normal limits. Abdominal examination is notable for a large pannus, and his liver edge is 2-cm inferior to his right costal margin. No masses or splenomegaly are noted. His lumbar paraspinous musculature is slightly tender, with moderate spasm, but there is no vertebral or sacroiliac tenderness. Rectal tone is normal, and prostate gland is not enlarged. His extremities reveal trace pitting edema, with normal pedal pulses. No xanthomata are present. Results of a neurologic examination are entirely normal.

Laboratory Examination

A chemistry panel reveals elevated levels of aspartate aminotransferase (AST, 57 IU/L) and alanine

aminotransferase (ALT, 65 IU/L), with bilirubin and alkaline phosphatase within normal limits. Fasting blood glucose is 114 mg/dL, and uric acid is above normal limits at 8.2 mg/dL. His cholesterol panel shows total cholesterol, 222 mg/dL; HDL cholesterol, 31 mg/dL; LDL cholesterol, 121 mg/dL; and triglycerides, 312 mg/dL. Thyroid function is normal. Urinalysis reveals no abnormalities.

- What NCEP-defined coronary risk factors are present?
- What is this patient's risk of CHD?

Recognizing Coronary Risk

The patient's presentation for evaluation of what is likely routine muscular low back pain offers an opportunity to identify and modify cardiovascular risk factors that are likely to impact his long-term health. The patient exhibits an elevated fasting glucose level, which although not considered a major risk factor according to NCEP, can be used to further intensify efforts at lipid lowering. This is justifiable given that patients with impaired fasting glucose levels (111–125 mg/dL) demonstrate significantly elevated coronary risk, with relative risk recently estimated at 56% higher than in patients with normal fasting glucose levels.²¹ In a study of close relatives of patients with type 2 diabetes, the presence of an impaired fasting glucose level predicted the metabolic syndrome as defined by World Health Organization criteria (presence of 2 or more of the following: hypertension, dyslipidemia, obesity, and microalbuminuria) in 42% to 64% of cases.^{8,22} Whether elevation in fasting plasma glucose is an independent risk factor for CHD is controversial, with major epidemiologic studies differing in their implications regarding this relationship.^{23–26}

Although his fasting glucose level is not a major CHD risk factor according to NCEP ATP-III guidelines, his low level of HDL cholesterol is (Table 1). Low levels of HDL cholesterol were the most predictive lipid parameter for the development of CHD in the Framingham Study²⁷; in men with HDL levels less than 35 mg/dL, the coronary disease risk was 90% higher than in those with HDL levels above 54 mg/dL.²⁸ His family history of premature coronary disease also is considered a major CHD risk factor.

His blood pressure is somewhat elevated, but not to the level ($\geq 140/90$ mm Hg) that is considered a major CHD risk factor by NCEP. The patient also has several NCEP-defined "life-habit" risk factors, including obesity and physical inactivity, the presence of which suggest the need to more aggressively treat his CHD risk. His triglycerides are significantly elevated and associated

Table 1. Major Risk Factors That Modify LDL Goals

- Cigarette smoking
- Hypertension (blood pressure $\geq 140/90$ mm Hg or on antihypertensive medication)
- Low HDL cholesterol (< 40 mg/dL)*
- Family history of premature CHD (CHD in male first-degree relative < 55 years; CHD in female first-degree relative < 65 years)
- Age (men ≥ 45 years; women ≥ 55 years)

CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Adapted from National Institutes of Health. Executive summary of 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). NIH Pub. No. 01–3670. Bethesda (MD): The Institutes; 2001. Available at: www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf. Accessed 26 Sep 2003.

*HDL cholesterol ≥ 60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

with increased CHD risk, but this is not thought to be an independent association in men.

- Based on these risk factors, what are this patient's lipid goals?

The NCEP identifies 3 risk categories, with different associated LDL goals.²⁰ Persons with 1 or no risk factors have an LDL goal of less than 160 mg/dL, persons with 2 or more risk factors have an LDL goal of either less than 130 mg/dL or less than 100 mg/dL, depending on absolute CHD risk, and persons with CHD or CHD-risk equivalents have a goal of less than 100 mg/dL. In patients with 2 or more risk factors, the NCEP guidelines suggest that absolute risk of CHD be calculated using Framingham risk scores.²⁰ A 10-year CHD risk calculated to be greater than 20% risk is considered a CHD-risk equivalent.

For the case patient, Framingham risk scoring predicts a less than 10% likelihood of CHD over the next 10 years; thus, his LDL cholesterol goal is less than 130 mg/dL. This risk estimate does not consider his mild abnormalities of blood pressure and fasting glucose, nor does it consider his obesity and family history. Therefore, his true CHD risk is likely to be considerably higher, especially over his entire lifetime. To address this discrepancy, the NCEP suggests more intensified LDL cholesterol reduction in patients, such as this one, who exhibit the metabolic syndrome (Table 2).

In addition to LDL, the NCEP guidelines suggest

Table 2. ATP-III Evidence Statements and Recommendations for Management of the Metabolic Syndrome

Evidence statements*

The presence of the metabolic syndrome accentuates the risk through accompanying elevated LDL cholesterol (C1). This increase in risk appears to be mediated through multiple risk factors—major and emerging risk factors (C1).

Clinical trials show that modifying 3 major components of the metabolic syndrome—atherogenic dyslipidemia (B2), hypertension (A2, B1), and the prothrombotic state (A2, B1)—will reduce risk for CHD.

Recommendations

Increased emphasis should be placed on therapeutic modification of the metabolic syndrome in persons undergoing LDL-lowering therapy. Primary management of the metabolic syndrome should be to reverse its root causes—overweight/obesity and physical inactivity. In addition, other lipid and nonlipid risk factors associated with the metabolic syndrome should be appropriately treated.

The presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-cholesterol goals are set with the major risk factors. Primary emphasis should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with the metabolic syndrome.

ATP-III = Adult Treatment Panel III; CHD = coronary heart disease; LDL = low-density lipoprotein.

Reprinted from National Institutes of Health. Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final Report. NIH Pub. No. 02–5215. Bethesda (MD): The Institutes; 2002. Available at: www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm. Accessed 26 Sep 2003:1127.

*Type and strength of evidence is shown in parentheses. A = major randomized controlled trials (RCTs); B = smaller RCTs and meta-analyses; C = observational and metabolic studies; 1 = very strong evidence; 2 = moderately strong evidence.

that non-HDL cholesterol be considered a secondary target when triglyceride levels exceed 200 mg/dL, with a goal level 30 mg/dL higher than the corresponding LDL level. Non-HDL cholesterol includes all of the atherogenic apolipoprotein B-containing lipoproteins, including triglycerides, remnant particles, and LDL. This patient has a non-HDL level of 191 mg/dL, more than 30 mg/dL above the NCEP non-HDL target of 160 mg/dL. The ATP-III guidelines do not suggest a specific goal for raising HDL.

- **How is the metabolic syndrome defined?**

Table 3. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	> 102 cm (> 40 in)*
Women	> 88 cm (> 35 in)
Triglycerides	> 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	> 130/85 mm Hg
Fasting glucose	110–125 mg/dL

Note: Diagnosis of the metabolic syndrome is made when 3 or more risk factors are present.

Reprinted from National Institutes of Health. Executive summary of 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). NIH Pub. No. 01–3670. Bethesda (MD): The Institutes; 2001. Available at: www.nhlbi.nih.gov/guidelines/cholesterol/atp3sum.pdf. Accessed 26 Sep 2003:16.

*Some men can develop multiple metabolic risk factors when the waist circumference is only marginally increased (ie, 94–102 cm [37–39 in]). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

The Complexity of the Metabolic Syndrome

The diagnostic features of the metabolic syndrome are shown in **Table 3**. The presence of at least 3 of the 5 characteristics is necessary to make the diagnosis. The characteristics are often coincident; indeed, this patient manifests all 5 of the criteria. The condition portends as significant a risk of premature CHD as does cigarette smoking.²⁹ Recognizing that risk factors in many patients often appear only marginally problematic, the NCEP recommends that the entire set of metabolic derangements be simultaneously targeted.

The pathophysiology of the metabolic syndrome involves abnormalities of glycemic control, body fat deposition, blood pressure, lipoproteins, coagulation factors, and vascular endothelial function and inflammation. The central cause(s) responsible for the dysregulation of these functions is still a subject of debate and may differ among patients. In most cases, there is impaired insulin function, known as insulin resistance.³⁰ In this setting, it is relatively common to see elevations in serum insulin and/or C peptide levels.³¹ As in this case, most patients with the metabolic syndrome exhibit

central obesity and low levels of HDL cholesterol.^{32,33} In women with this syndrome, the HDL cholesterol level may only be mildly reduced.³⁴ Insulin resistance also is associated with both hypertension³⁵ and high-normal blood pressure levels.³⁶ Levels of C-reactive protein, an inflammatory marker, tend to be higher in patients with the metabolic syndrome.^{37,38} There are also genetic factors, and the disorder is somewhat more common among Hispanic, Asian, and African American patients.

- **Is additional testing indicated in this patient?**

Case Patient—Additional Laboratory Testing

History, examination, and laboratory testing have largely ruled out secondary causes of the case patient's dyslipidemia, although his liver function test abnormalities are of some concern. The patient's alcohol consumption might be contributing to the mild transaminase elevations, although the pattern (ALT > AST) is somewhat atypical. Another diagnosis to be considered is a condition called nonalcoholic steatohepatitis, also known as fatty liver, which is commonly associated with obesity and/or hypertriglyceridemia. To make this diagnosis, other forms of liver disease, such as viral or other forms of hepatitis, should be excluded. In addition to serologic testing, a hepatic ultrasound often can be helpful in demonstrating the presence or absence of fatty infiltration of the liver. In this patient's case, an ultrasound confirmed steatohepatitis, and testing was negative for hemochromatosis and hepatitis B and C.

Formal screening for diabetes should be considered beyond measuring the fasting glucose level. A recent review suggests that 2-hour postprandial glucose levels are more sensitive for the presence of diabetes and microvascular risk in this setting.³⁹ A glycosylated hemoglobin measurement or equivalent assessment of long-term glycemic control is logistically easier to obtain but is less sensitive. A urinary albumin/creatinine ratio or equivalent measurement of microalbuminuria can be helpful in assessing the need for certain drug therapies in this setting. Of the individual components of the metabolic syndrome, microalbuminuria confers the strongest risk of cardiovascular death.⁸

The patient's uric acid level, included in the chemistry panel ordered by the physician, is modestly elevated, although he had no symptoms of gout or history of kidney stones. A large prospective ambulatory study found that elevated uric acid levels, a relatively common feature of patients with the metabolic syndrome, is independently and significantly associated with cardiovascular risk.⁴⁰ Other studies have not found that the association is independent of other variables, however.

Although it is quite likely that this patient could have abnormal results with additional coronary risk testing (eg, C-reactive protein levels, lipoprotein electrophoresis, or coronary electron-beam computed tomography), these tests are not recommended by the NCEP in this circumstance. The results of such tests would not alter the treatment plan, as the patient is already judged to be at increased risk of cardiovascular disease and therefore a candidate for aggressive intervention.

Case Patient—Initial Management

The patient is prescribed ibuprofen 600 mg 3 times daily as needed and back strengthening exercises for his pain. At a follow-up visit 4 weeks later, the patient reports that his back pain has significantly improved. At this visit, the primary care physician reviews the laboratory findings with him. She explains that his long-term risk for heart disease is high and that a variety of risk factors will need to be targeted. After writing out the key elements of his lifestyle changes, she notes that he will need to play an active role in his treatment plan. In addition to resuming a more regular aerobic exercise program (30 minutes of moderate physical activity 3 to 4 times weekly), she suggests that he modify his diet by eating fish several times per week and increasing his consumption of vegetables and foods high in soluble fiber content, such as beans and oat bran. Weight loss will be needed to improve his coronary risk as well as his liver inflammation, so the physician provides a referral to a dietitian to assist him with food selection and portion sizing. She states that a reasonable weight loss goal would 10% of his current weight, or 24 lb, at a reduction rate of 1 to 2 lb per week. A follow-up visit is scheduled for 6 weeks; the patient is asked to have a fasting lipid and liver panel drawn a few days prior to the visit if possible.

- **What is the role of nonpharmacologic treatment in the metabolic syndrome?**

Lifestyle Modification

The initial management of the metabolic syndrome should be primarily focused on effective lifestyle modification. In the NCEP guidelines, "therapeutic lifestyle changes" or "TLC" involve a multifaceted approach at dietary improvement, regular exercise, and weight loss (**Figure 1**). Among its recommendations, the TLC diet limits dietary fat to no more than 30% of total calories and is particularly restrictive of saturated fat sources such as meats and hydrogenated oils. In place of these fats, monounsaturated fats are emphasized, to a maximum

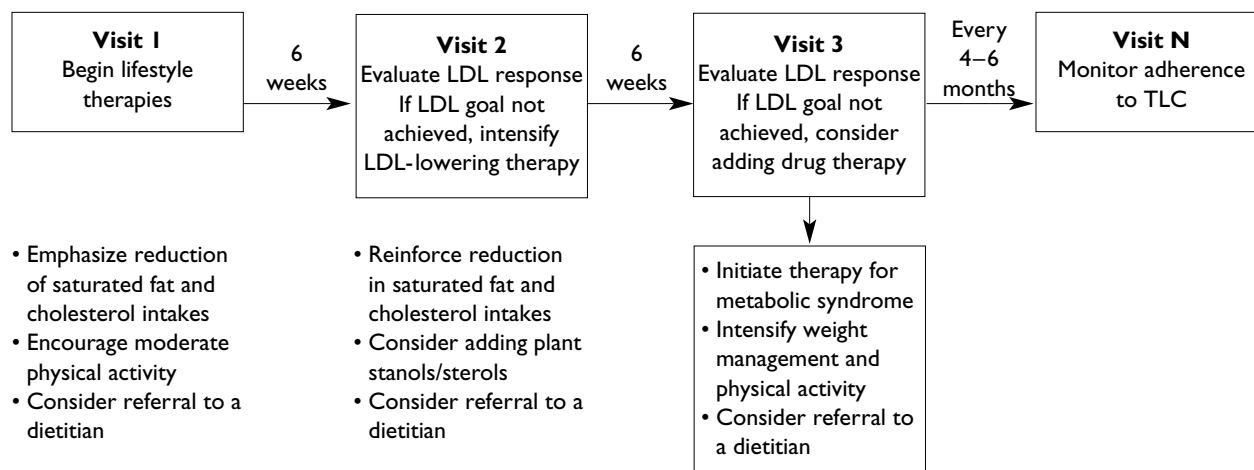


Figure 1. Integration of therapeutic lifestyle changes (TLC) in management of the metabolic syndrome. LDL = low-density lipoprotein. (Reprinted from National Institutes of Health. Executive summary of the Third report of the National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III]. NIH Pub. No. 01–3670. Bethesda [MD]: The Institutes; 2001. Available at: www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf. Accessed 26 Sep 2003:120.)

of 20% of total daily calories. Monounsaturated fatty acids, such as olive oil and canola oil, do not impair insulin function; in contrast, saturated fatty acids reduce insulin activity even in healthy subjects.⁴¹ Polyunsaturated fats, such as fish oil and flaxseed oil, also can play a role in the management of dyslipidemia associated with the metabolic syndrome. Consumption of coldwater fish, such as salmon and tuna, which are rich in omega-3 fatty acids, will lower triglycerides and has been linked to decreased cardiovascular mortality.⁴² Fish oil supplements (capsules) can decrease levels of triglycerides by up to 39%.⁴³

Besides choosing appropriate fat sources, the ATP-III recommends a number of other dietary interventions as part of TLC. Substitution of plant stanol or sterol ester products for butter or margarine spreads is suggested and may reduce total and LDL cholesterol levels by up to 10%.⁴⁴ Increased soluble fiber intake also is recommended as a means to limit intestinal cholesterol absorption. Weight reduction and exercise are particularly important forms of lifestyle modification in this patient population, as both lessen insulin resistance.^{45,46} TLC offers patients the means to address the root causes of the syndrome, and improve many, if not all, of the derangements in a relatively inexpensive fashion. If TLC is insufficient to reverse the clinical manifestations of the syndrome, then drug therapy should be strongly considered for management—and possibly prevention—of associated CHD risk factors.

• **What are this patient’s lipid goals given the presence of the metabolic syndrome?**

According to the NCEP ATP-III guidelines, “the presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL goals are set with the major risk factors” (Table 2). In this setting, with high serum triglycerides and a low HDL cholesterol level, the patient is likely to have an atherogenic lipid particle distribution.⁴⁷ The smaller, denser LDL particles in this pattern (sometimes referred to as phenotype “B”) are associated with increased CHD risk at lower LDL cholesterol concentrations than in patients with more buoyant forms of LDL. Indeed, the NCEP recommendations note that “there is little doubt that this syndrome taken in aggregate enhances the risk for CHD at any given cholesterol level.” In this regard, one could effectively argue for lipid targets for this patient comparable to those for patients with established CHD: LDL less than 100 mg/dL and non-HDL less than 130 mg/dL. Clearly, his entire lipid profile must be targeted along with other elements of his metabolic syndrome.

Case Patient—Follow-Up

The patient is somewhat successful in increasing his exercise and decreasing sources of simple carbohydrates and saturated fats. As a result, he loses 12 lb over the next 6 weeks, achieving a weight of 225 lb (102 kg) and a body mass index of 32 kg/m². His blood pressure (131/82 mm Hg), fasting blood glucose (102 mg/dL),

and transaminase levels (AST, 43 IU/L and ALT, 41 IU/L) similarly improve. The hemoglobin A_{1c} is 5.8% (upper end of normal range, 5.9%). The lipid profile is as follows: total cholesterol, 213 mg/dL; HDL cholesterol, 32 mg/dL; LDL cholesterol, 109 mg/dL; and triglycerides, 261 mg/dL. His physician encourages him to continue these healthy lifestyle practices to further reduce his cardiovascular risk. In addition, she recommends that he begin simvastatin 20 mg daily and aspirin 81 mg daily.

- **What is the role of lipid-lowering medication in the metabolic syndrome?**

Clinical Trials of Lipid-Lowering Medications

The patient showed improvement in his metabolic profile with therapeutic lifestyle changes, although TLC did not achieve target lipid levels for either LDL cholesterol or non-HDL cholesterol. In addition to modification of lifestyle, the use of lipid-lowering medication in the metabolic syndrome significantly improves lipid profiles and reduces vascular events. Subset analyses of the statin trials have shown statins to be at least as beneficial in reducing cardiovascular events and mortality in subjects with the metabolic syndrome as in those without the condition. However, absolute risk reduction is greater in those with impaired compared with normal fasting glucose tolerance because of the higher event rates in the former circumstance.^{48,49} Post hoc analysis of patients with impaired fasting glucose levels who were enrolled in the Scandinavian Simvastatin Survival Study, for example, revealed that simvastatin treatment (compared with placebo) was associated with marked reduction in hospitalization for myocardial infarction (44%), hospitalization for CHD (35%), and hospitalization for cardiovascular disease (30%).⁵⁰ Over the course of the 5-year trial, savings from decreased hospitalization offset 74% of the medication cost in patients with the metabolic syndrome.⁵¹

Interestingly, statins may delay or prevent the onset of diabetes in high-risk patients as well. Treatment of middle-aged hyperlipidemic men with pravastatin versus placebo was associated with 30% decrease in the likelihood of developing diabetes mellitus during the 5-year West of Scotland Coronary Protection Study.⁵² Although this observation was post hoc, it suggests that statin therapy may act directly or indirectly to improve insulin resistance. This result may partially explain the favorable effects of statins in patients with impaired fasting glucose levels.

Besides the statins, the fibrates offer favorable effects on the lipid profiles and coronary risk of patients with

the metabolic syndrome. The Helsinki Heart Study (HHS) found that gemfibrozil treatment was associated with a 34% relative risk reduction versus placebo in coronary events in middle-aged men with dyslipidemia. Post hoc analysis of HHS revealed that the subgroup with baseline triglycerides greater than 200 mg/dL and HDL cholesterol less than 35 mg/dL enjoyed a 67% relative risk reduction compared to placebo.⁵³ Whereas the overall results of the Bezafibrate Intervention Program trial were neutral, bezafibrate treatment was associated with a 42% relative risk reduction in coronary events in a similarly hypertriglyceridemic subgroup. Lastly, the Veterans Affairs HDL Intervention Trial reported that gemfibrozil 1200 mg daily was associated with a 22% relative risk reduction in coronary events over placebo in male patients with CHD and HDL cholesterol less than 40 mg/dL. Together, the clinical trials of lipid-lowering medication in patients with insulin resistance and/or hypertriglyceridemia suggest that there is benefit in reducing both LDL cholesterol and triglycerides in this patient population.

- **What is the role of combination lipid-lowering therapies in treatment of the metabolic syndrome?**
- **What other medical therapies should be considered in the management of the metabolic syndrome?**

Combination Therapy

Because of their differing mechanisms of action and proven cardiovascular benefits, statins and fibrates are recommended by some authorities as a valuable combination treatment to reduce risk of cardiovascular disease in patients with the metabolic syndrome.²⁰ This combination does carry with it a small risk of rhabdomyolysis and is therefore suggested with some caution. Whereas statin monotherapy is effective at reaching LDL cholesterol goals, it is often insufficient in achieving non-HDL goals owing to persistent hypertriglyceridemia. Conversely, the fibrates reduce triglycerides levels substantially but have minimal effects on LDL cholesterol concentration, sometimes even slightly increasing LDL cholesterol. For these reasons, the combination is justifiable in appropriate patients when TLC and monotherapy fail.

The use of niacin in combination with statins is appealing, especially in light of the recent finding of the HDL Atherosclerosis Treatment Study, in which a combination of niacin and simvastatin reduced coronary events by 70% versus placebo.⁵⁴ The population studied displayed a lipid phenotype typical of patients with the metabolic syndrome, with baseline HDL of 31 mg/dL and triglycerides of 213 mg/dL. While there

is some apprehension about increased risk of hepatitis and/or myositis with the use of a statin in combination with niacin, concern regarding the adverse glycemic effects of niacin was quelled somewhat by the recent Arterial Disease Multiple Intervention Trial.⁵⁵ In this study, the use of moderate doses of niacin in patients with well controlled diabetes mellitus did not significantly worsen glycemic parameters. As a rule, the use of bile acid resins and/or hormone replacement in patients with the metabolic syndrome is relatively contraindicated because of the triglyceride-raising properties of these therapies.

Additional Medical Options

In addition to lipid-lowering treatments, there may be some role for other medical therapies in reducing the effects of the metabolic syndrome. Blood pressure control is strongly recommended in this population by both the NCEP and JNC-VI.^{20,56} Based on the reduced incidence of vascular events and diabetes in normotensive patients at high risk for CHD that was associated with ramipril treatment compared to placebo in the Heart Outcomes Protection study, it seems quite possible that there is specific ability of angiotensin-converting enzyme (ACE) inhibition therapy to moderate the clinical manifestations of insulin resistance.⁵⁷ Whether angiotensin-receptor blockade would result in benefits similar to ACE inhibition remains to be seen. Similarly, studies evaluating the role of insulin sensitizers (eg, thiazolidinediones) in treatment of patients with metabolic syndrome are underway. These agents have been shown to decrease glucose levels, insulin concentrations, blood pressure, and thrombotic markers while improving dyslipidemia and decreasing carotid artery intima medial thickness in insulin-resistant subjects.⁵⁸ In a study of nearly 200 patients with type 2 diabetes mellitus, pioglitazone monotherapy significantly reduced serum triglycerides (–17%) and raised HDL (+13%) versus placebo.⁵⁹ Aspirin therapy is generally recommended by the NCEP as it might also be helpful in reducing the proinflammatory state, but this has not been well studied in either the metabolic syndrome or in women without established CHD.⁶⁰

Case Patient—6 Weeks Later

After 6 weeks on simvastatin, the patient's lipid profile improves to total cholesterol, 169 mg/dL; HDL cholesterol, 34 mg/dL; LDL cholesterol, 84 mg/dL; and triglycerides, 224 mg/dL.

- **What are next steps in the treatment of this patient?**

After starting low-dose statin therapy to control LDL cholesterol, the treating physician has a number

of options for further care, including intensifying his lifestyle changes and/or statin therapy and the addition of a fibrate, fish oil, or niacin.

Although each of these treatments would likely improve the patient's metabolic profile and cardiovascular risk, the safest options are intensified lifestyle changes and fish oil. In this case, the patient was successful in making beneficial nonpharmacologic modifications and these should be encouraged. In the event that his laboratory profile remains inadequately controlled, most lipid treatment experts would suggest either increasing his statin strength/dosage or adding a fibrate (fenofibrate appears to have less risk of rhabdomyolysis in combination with statins than does gemfibrozil).

Case Patient—6 Months Later

The patient returns for follow-up with weight, blood pressure, blood sugar, and lipid profile essentially unchanged. While his physician continues to emphasize that he focus on the lifestyle changes, she also increases his simvastatin to 40 mg daily. Six weeks later, his lipid profile is measured at total cholesterol, 151 mg/dL; HDL cholesterol, 33 mg/dL; LDL cholesterol, 76 mg/dL; and triglycerides, 216 mg/dL. He has met his LDL cholesterol and non-HDL goals of 100 mg/dL and 130 mg/dL, respectively. Although he has achieved these goal levels, the NCEP still classifies his triglyceride level as high, and it should be regularly addressed in follow-up.

- **What medical therapies are being developed that may have a potential role in the management of the metabolic syndrome?**

Future Therapies

Considerable efforts are currently underway to develop an agent in the class of peroxisome proliferator activator receptor agonists (thiazolidinediones and others) that have favorable effects on both glycemic and lipid profiles in patients with insulin resistance. As well, new therapies such as the selective cholesterol absorption inhibitors (eg, ezetimibe) or more potent statins (eg, rosuvastatin) should assist practitioners in achieving lipid targets in such patients.^{61,62} Lastly, inhibition of the enzyme cholesteryl ester transfer protein with the agent JTT-705 has been shown to markedly increase levels of HDL cholesterol and reduce atherosclerosis in rats.⁶³ While this is unlikely to be studied in humans immediately, it offers a novel pathway through which to improve the lipid profile of patients with low levels of HDL cholesterol, such as in the metabolic syndrome.

CONCLUSION

Patients with the metabolic syndrome are at substantially increased risk for cardiovascular disease despite having only mild-appearing metabolic derangements. The condition is usually asymptomatic, and affected patients may present for evaluation of unrelated complaints. The successful treatment of the metabolic syndrome often requires multiple interventions, both lifestyle-based and pharmacologic. Aggressive behavioral interventions such as TLC are key to improving the underlying cardiovascular profile of patients with the syndrome. In treating the dyslipidemia associated with this disorder, attention should be primarily focused on reducing LDL cholesterol to NCEP ATP-III goals, and secondarily on achieving non-HDL goals. **HP**

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