REVIEW

CME CREDIT

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A truly deadly quartet: obesity, hypertension, hypertriglyceridemia, and hyperinsulinemia

ABSTRACT

The cluster of hypertriglyceridemia, hyperinsulinemia, obesity, and hypertension markedly increases the risk of coronary artery disease. Although no treatments target this syndrome specifically, treatment of each aspect of the cluster is important. Prevention—weight loss and physical activity—is key.

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The National Cholesterol Education Program recognizes the importance of the metabolic syndrome and has published guidelines for its diagnosis.

Weight loss, physical activity, and treatment of the individual risk factors constitute the main strategies for treatment.

For now, the goals and methods of treating hypertension and dyslipidemia are the same in people with the metabolic syndrome as in the general population.

Thiazolidinedione drugs increase insulin sensitivity, but their use in the metabolic syndrome is only speculative at present. We recommend they be used only as indicated to treat diabetes mellitus.

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This paper discusses treatments that are not approved by the US Food and Drug Administration for some of the uses under discussion.

WE NOW KNOW that the metabolic syndrome of hypertension, obesity, hyperinsulinemia, and hypertriglyceridemia can truly be called the "deadly quartet."

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People with this cluster, especially women,[1] face a heightened risk of coronary disease and death, even after coronary artery bypass grafting.[2]

Treatments specifically targeting the deadly quartet are lacking. The best available treatment is prevention: living a healthy lifestyle by controlling one's weight, exercising regularly, stopping smoking, and eating a healthy diet.

Still, treating each individual element of the cluster remains an important secondary strategy.

A WIDESPREAD PROBLEM

This cluster of risk factors, first described by Reaven in 1988,[3] has variously been called the *deadly quartet*, the *metabolic syndrome*, *syndrome X*, and *insulin resistance syndrome*.

Elements of the syndrome are common and interrelated. For example:

- At least 10% of patients with coronary artery disease have three of the four factors.
- Ten million people in the United States have diabetes, and another 5 1/2 million are believed to have undiagnosed diabetes.
- One third of US adults are estimated to be

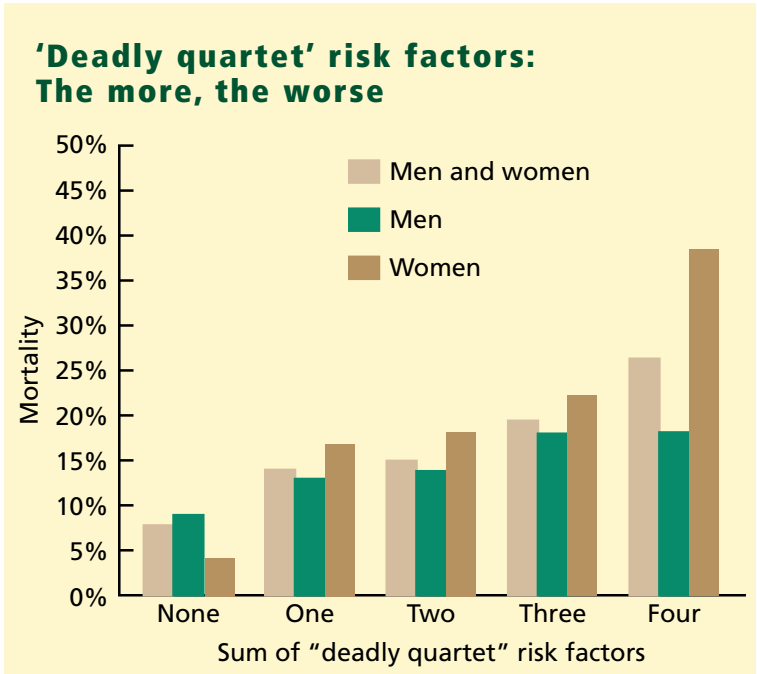

FIGURE 1. All-cause mortality (median 8-year follow-up) in 6,428 patients who underwent coronary artery bypass grafting at The Cleveland Clinic Foundation between 1987 and 1992, according to number of "deadly quartet" risk factors (obesity, diabetes mellitus, hypertension, hypertriglyceridemia).

FROM SPRECHER DL, PEARCE GL. HOW DEADLY IS THE "DEADLY QUARTET"? A POST CABG EVALUATION. J AM COLL CARDIOL 2000; 36:1159–1165.

overweight or obese, ie, with a body mass index higher than 25.[4] People who are obese are at least twice as likely to have hypertension, hypertriglyceridemia, or type 2 diabetes mellitus than people who are not obese.

- People with hypertension have a twofold higher prevalence of diabetes and obesity compared with normotensive people,[5] and half are insulin-resistant.[6]

Syndrome factors are also common in polycystic ovarian disease, a condition with a high incidence of atherosclerosis.

Ford et al[7] analyzed data from the third National Health and Nutrition Examination Survey and estimated that the prevalence of the metabolic syndrome in the US population is 21.8%, increasing with age from 6.7% among people aged 20 through 29 years to 43.5% in those aged 60 through 69 years.

A RISKY QUARTET, ESPECIALLY FOR WOMEN

Wilson et al[8] looked at a community sample of nearly 5,000 men and women in the Framingham offspring study and found that 17% had at least three of six metabolically linked risk factors: low levels of high-density lipoprotein cholesterol (HDL) or high total cholesterol, triglycerides, systolic blood pressure, body mass index, or glucose.

Men with three or more of these factors had a relative risk of coronary artery disease of 2.39 (95% confidence interval 1.56–3.36); in women the number was 5.9 (95% confidence interval 2.54–13.73). The authors estimated that nearly half of coronary events in women and one fifth in men can be attributed to clusters of these factors.

Sprecher and Pearce[2] examined survival in 6,428 patients who underwent coronary artery bypass grafting. In a median follow-up of 8 years, 860 patients died. Of those who died, 9 in 10 had at least one quartet factor.

Ten percent of the men and 21% of the women had at least three of the four factors, and of these, 1 in 5 men and 1 in 4 women died. Men who had all four risk factors had a twofold to threefold higher risk of dying, and women had a tenfold higher risk (FIGURE 1). No single factor seemed pivotal.

CAUSE UNKNOWN, BUT THERE ARE CLUES

The basis for the metabolic syndrome is unknown, but we have clues as to how it develops and how it leads to coronary artery disease (FIGURE 2).

Insulin resistance, a multisystem disorder involving genetics, obesity, physical inactivity, and advancing age, may be the initiator of both type 2 diabetes mellitus and the metabolic syndrome.

Reaven[9] suggests that, in patients with insulin-resistant type 2 diabetes mellitus, hyperglycemia develops only when hyperinsulinemia can no longer be sustained. Apparently, not only do the body cells lose their sensitivity to insulin, but pancreatic beta cells can no longer compensate by producing more insulin.

How insulin resistance leads to coronary disease

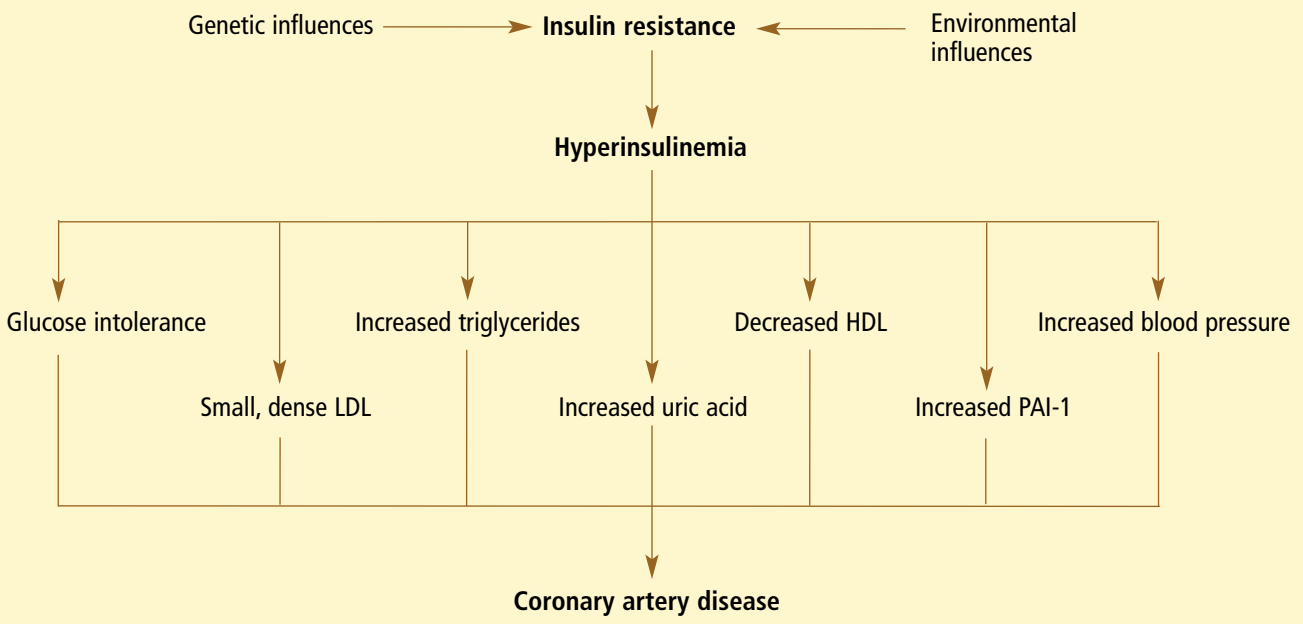

FIGURE 2. Schematic description of the proposed relationship between factors leading to insulin resistance, the various factors comprising the metabolic syndrome, and coronary artery disease. HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, PAI-1 = plasminogen activator inhibitor 1.

FROM REAVEN GM. PATHOPHYSIOLOGY OF INSULIN RESISTANCE IN HUMAN DISEASE. PHYSIOL REV 1995; 75:473–486.

Insulin receptor insensitivity and postreceptor defects may alter intracellular signaling and other factors related to vascular toxicity.

Hyperinsulinemia per se may increase the activity of the sympathetic nervous system and increase reabsorption of sodium in the proximal renal tubules, decreasing urinary sodium excretion; both lead to high blood pressure.

Disordered lipid metabolism. Lipoprotein lipase, a key enzyme in fat breakdown, is insulin-sensitive. Decreased levels are found in people with diabetes or insulin resistance,[10] and result in elevated triglycerides and reduced HDL.

Hyperglycemia. With higher levels of glucose in the blood, more low-density lipoprotein cholesterol (LDL) is glycated. Glycation enhances the affinity of LDL for modified LDL receptors on macrophages, a process that promotes foam cell formation,[11,12] endothelial cell cytotoxicity,[13] and smooth muscle proliferation.

Prothombotic state. Plasminogen activator inhibitor 1 (PAI-1) is elevated in the metabolic syndrome.[14] Increased levels have been associated with coronary artery disease and myocardial infarction.[15]

Inflammation. C-reactive protein (CRP), a systemic marker of inflammation, progressively increases with the number of metabolic syndrome factors.

Increasing evidence indicates that visceral fat contributes to the inflammatory pathway response, involving phospholipase A2, CRP, and intracellular adhesion molecule, which are emerging markers of coronary artery disease.[16]

TABLE 1

Diagnosis of the metabolic syndrome

RISK FACTOR (AT LEAST 3 REQUIRED FOR DIAGNOSIS)	DEFINING LEVEL
Abdominal obesity	Waist circumference
Men	> 102 cm (40 in)
Women	> 88 cm (35 in)
Triglycerides	≥ 150 mg/dL
High-density lipoprotein cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130 / ≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL

FROM THE EXPERT PANEL ON DETECTION, EVALUATION AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS. 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). JAMA 2001; 285:2486–2497.

Exercise:
- **Decreases insulin resistance**
- **Lowers VLDL**
- **Raises HDL**
- **Lowers blood pressure**

DIAGNOSING METABOLIC SYNDROME

The National Cholesterol Education Program recognizes the importance of the metabolic syndrome in its 2001 Adult Treatment Panel III guidelines[17] and identifies it as a secondary target of risk reduction therapy. The diagnostic criteria (TABLE 1) are easy to use. (Fasting glucose levels, rather than insulin levels, are used as a criterion for diagnosis.)

MANAGEMENT

The options for treatment of the deadly quartet are limited. Prevention is the best strategy: the best options are to maintain a healthy lifestyle by keeping one's weight down, engaging in regular exercise, not smoking, and following a healthy diet.

Treatment of each aspect of the cluster is an important secondary strategy and includes fibrates for hypertriglyceridemia and low HDL, receptor-active drugs for diabetes, and angiotensin-converting enzyme (ACE) inhibitors for their antihypertensive and other beneficial properties.

Promote diet and exercise

Physical activity and weight loss effectively reduce all the risk factors of the syndrome. Wilson et al[8] found that a weight loss of only 2.25 kg (5 lb) was highly associated with a decrease in the number of risk factors ($P < .0001$), while a weight gain of the same amount had the opposite effect.

Regular physical activity decreases insulin resistance, reduces levels of very-low-density lipoprotein (VLDL), increases HDL, lowers blood pressure, lowers LDL (in some people),[18,19] and improves cardiovascular function.[20,21] Weight loss and regular exercise also reduce the risk for new-onset type 2 diabetes mellitus.[22,23]

Nutrition guidelines from the American Diabetes Association include extensive references on how diet affects metabolic syndrome risk factors.[24] Patients and health professionals can also find recommendations for weight loss and obesity treatment at the web site of the Obesity Education Initiative of the National Heart, Lung, and Blood Institute.[25]

The role for antiobesity agents remains unknown.

Treat hypertension and dyslipidemia

Treatment of hypertension and dyslipidemia has been shown to improve outcomes in patients with diabetes.

ACE inhibitors seem to have beneficial effects independent of blood pressure lowering.[26] They are valuable in preventing diabetic nephropathy, and data from the Heart Outcomes Prevention Evaluation (HOPE) study[27] indicate that they may even prevent the onset of diabetes itself. Data are also emerging about possible anti-inflammatory effects of these drugs.

Statins. The uses of statins in coronary artery disease are also well established. In a post hoc analysis of the Scandinavian Simvastatin Survival Study, Ballantyne et al[28] found that patients with the combination of high LDL levels, low HDL levels, and elevated triglycerides were more likely than patients with high LDL elevations alone to have other elements of the metabolic syndrome, and they benefited more from simvastatin therapy.

ACE inhibitors and statins may be used in the future specifically to manage the metabolic syndrome. However, for now, the goals and methods of treatment of hypertension and dyslipidemia in the general population apply to

patients with the metabolic syndrome as well.

Should insulin resistance be targeted?

It is unclear whether specific treatment of insulin resistance may reduce the risk of developing coronary artery disease, but if insulin resistance is central to the cause of the metabolic syndrome, research in this direction is worth pursuing.

Thiazolidinediones, a new class of medications called insulin sensitizers, are effective in controlling glucose levels in insulin-resistant diabetic patients and also have a modestly favorable effect on triglyceride and HDL levels. Although weight gain is common, there is evidence that visceral fat is redistributed to abdominal fat, which may not be as bad. Furthermore, small studies suggest these agents may slow the progression to type 2 diabetes mellitus in patients with gestational diabetes.[29]

Thiazolidinedione treatment may also lower PAI-1, which is elevated in the metabolic syndrome.[30] However, at this point, thiazolidinedione use should not be considered standard practice outside of properly selected patients with type 2 diabetes mellitus.

Metformin has also been reported to reduce the risk of new-onset diabetes mellitus,[22] acting by reducing hepatic glucose production rather than diminishing insulin resistance.[31] Until proven otherwise, its main role is in the management of hyperglycemia in diabetic patients and not in the treatment of insulin resistance.

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