

# ACTUAL CONCEPTIONS IN MANAGEMENT OF METABOLIC SYNDROME. PERSPECTIVES IN PROPHYLAXIS AND THERAPY

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## REZUMAT

Sindromul metabolic este recunoscut ca factor de risc semnificativ pentru dezvoltarea bolii coronariene. La pacienții cu sindrom metabolic prevenția bolii coronariene și/sau a diabetului zaharat tip 2 se poate face numai cu un tratament multidisciplinar, combinat cu schimbarea stilului de viață și ameliorarea profilului lipidic. Tratamentul sindromului metabolic se adresează fiecărei entități componente în parte. Bolnavul cu sindrom metabolic trebuie protejat prin exercițiu fizic, scădere în greutate, reducerea valorilor tensionale și ale glicemiei, reducerea LDL-colesterolului și prin protecția endotelială medicamentoasă.

**Cuvinte cheie:** sindrom metabolic, rezistență la insulină, dislipidemie, tratament, dietă

## ABSTRACT

The metabolic syndrome is increasingly recognized as a strong predictor of patient risk for developing coronary heart disease. Multidisciplinary treatment combining therapeutic lifestyle counseling with lipid-altering pharmacotherapy is recommended to prevent or delay the development of coronary heart disease and/or type 2 diabetes in patients with metabolic syndrome. Management of the metabolic syndrome requires treatment of many of the individual metabolic consequences present in each individual. The patient with metabolic syndrome should be protected through physical activity, weight loss management, blood pressure and blood glucose reduction, decrease of LDL-cholesterol and through endothelial pharmacotherapy protection.

**Key Words:** metabolic syndrome, insulin resistance, dyslipidemia, therapy, diet, MetS

## BACKGROUND

The metabolic syndrome (MetS) is based on six major components: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, a proinflammatory state, and a prothrombotic state. In order, it is a constellation of abnormal glucose and lipid metabolism that has reached epidemic proportions over the past decade - with more than 1 in 4 adults affected by this disorder.<sup>1</sup> Patients with the metabolic syndrome are a 2- to 4-fold increased risk of stroke and a 3- to 4-fold increased risk of myocardial infarction compared with those without the metabolic syndrome.<sup>2</sup>

What then of management? Does the treatment of the metabolic syndrome differ from the treatment of its individual components? Debates continue about the best approach for management of metabolic syndrome.

The approach to the treatment of the metabolic syndrome is heavily dependent upon which concept of the metabolic syndrome is believed. If one believes that environmental factors such as obesity and decreased physical activity are the fundamental causes of the metabolic syndrome in most individuals in western society, as in the NCEP guidelines, then most of the efforts will be to reduce obesity and increase physical activity. If one believes that insulin resistance is the underlying cause of the metabolic syndrome, as in the WHO definition, then one might decrease insulin resistance either by behavioral measures or pharmacological interventions. If one believes that the major increase in cardiovascular risk is related to the underlying cardiovascular risk factors, then one would focus mainly on the treatment of the underlying cardiovascular risk factors.<sup>3</sup>

We may organize the clinical management in two broad areas, therapeutic lifestyle changes and

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pharmacologic therapy, focused on two major goals: prevention of Type 2 Diabetes and reduction of clinical coronary cardiovascular events.

Currently, no randomized controlled trials specifically examining the treatment of metabolic syndrome have been published.

Because the root causes of the metabolic syndrome (overweight/obesity and physical inactivity) are reversible and the individual components of the metabolic syndrome are modifiable, recognition of the metabolic syndrome provides a great opportunity for risk reduction.<sup>4</sup> Management of the metabolic syndrome consists primarily of two strategies: modification or reversal of the root causes, including weight reduction and increased physical activity, and direct treatment of the metabolic risk factors, including atherogenic dyslipidemia, elevated blood pressure, the prothrombotic state, and underlying insulin resistance. All of the components of the metabolic syndrome may be improved with weight reduction and increased physical activity. Based on clinical trials, aggressive management of the individual components of the syndrome should make it possible to prevent or delay the onset of diabetes mellitus, hypertension, and cardiovascular disease.<sup>5</sup>

## **THERAPEUTIC LIFESTYLE CHANGES**

In terms of therapeutic objectives, number one is to reduce the underlying causes through therapeutic lifestyle changes (TLC) as defined by the new guidelines, which include diet to reduce caloric intake and to correct the obesity, the overweight condition, and physical activity to correct the condition caused by sedentary life. Therapeutic lifestyle interventions, including weight management and increased physical

activity, are the cornerstone for management and should be encouraged throughout a patient's care. Smoking cessation should be strongly encouraged.

Weight loss is a key therapeutic objective. All components of the metabolic syndrome are positively affected by weight loss. Even modest weight reductions, in the range of 5% to 10% of initial body weight, are associated with significant clinical improvements in a wide range of comorbid conditions.<sup>6</sup>

Weight loss and increased physical activity have been shown by the Diabetes Prevention Program to reduce the risk of Type 2 Diabetes by 58%.<sup>7</sup> This reduction was greater than that seen with metformin in subjects with impaired glucose tolerance (25%).

TLC includes the following: (a) reduced intakes of saturated fats and cholesterol, (b) therapeutic dietary options to enhance LDL lowering (plant stanols/sterols and increased viscous fiber), (c) weight control, and (d) increased physical activity.

The TLC treatment model provides an evidence-based approach to weight control and fitness. (Table 1)

Consensus panels including ATP III recommend multidisciplinary therapeutic lifestyle counseling as first-line treatment for metabolic syndrome: increased physical activity (~30 minutes of brisk walking daily) in the 70% of Americans who are sedentary; a reduced-energy (~500-1000 cal/day reduction) low-fat, low-trans-fat, low-cholesterol, high-complex-carbohydrate (CHO) diet, possibly with isocaloric substitution of unsaturated fats for CHO for weight loss in obese patients; and incorporation of physical activity, stress management, and group support for effective long-term weight management.<sup>8</sup>

No single diet is currently recommended for patients with metabolic syndrome; therefore, it may be best for physicians to focus on each patient's specific

**Table 1.** The Therapeutic Lifestyle Change (TLC) model adapted for metabolic syndrome (adapted from Ref. 8).

	6 wks	6 wks	6 wks	Every 4-6 mos
<b>Visit 1</b>	<b>Visit 2</b>	<b>Visit 3</b>	<b>Visit 4</b>	<b>Visit N</b>
Weight reduction	Evaluate weight, WC, LDL, HDL-C, Trig, BP, glucose	Evaluate weight, WC, LDL, HDL-C, Trig, BP, glucose	Evaluate weight, WC, LDL, HDL-C, Trig, BP, glucose	Monitor the adherence to TLC and (if indicated) medication
	⇓		⇓	⇓
Encourage ↑ physical activity		Reinforce dietary changes + ↑ physical activity		If no improvement in parameter of MS, consider drug therapy
Refer to RD for diet to ↓ weight, BP, blood lipids, glucose		Consider meal replacement		Intensify weight management and physical activity

metabolic alterations when offering dietary advice. Sustained dietary changes may require referral to a registered dietitian to help implement suggestions and ensure adequate micronutrient intake (e.g., calcium, iron, folate) while reducing calories. There is debate about what proportions of macronutrients (i.e., protein, fat, and carbohydrates) will produce the best outcome (low-fat, low-carbohydrate, or Mediterranean diets). If a patient is consuming fewer calories than he or she is expending, the macronutrient composition of the diet is probably of secondary importance, because weight loss improves metabolic syndrome.

According to the Dietary Approaches to Stop Hypertension (DASH) study, patients who consumed a diet low in saturated fat and high in carbohydrates experienced a significant reduction in blood pressure, even without weight reduction. The DASH diet emphasizes fruits, vegetables, low-fat dairy foods, whole grains, poultry, fish, and nuts, while reducing saturated fats, red meat, sweets, and sugar-containing beverages. Reducing sodium intake can further reduce blood pressure or prevent the increase in blood pressure that may accompany aging

The long-term effects of low-carbohydrate diets have not been studied adequately, but in the short-term, these diets have been shown to lower triglyceride levels, raise HDL-cholesterol levels, and reduce body weight.

Both low-fat, high-carbohydrate diets and high-monounsaturated fat diets improve coronary disease profile.<sup>9</sup> The key to all positive long-term dietary changes, however, is to increase servings of fruits, vegetables, and high-fiber whole grains and to displace intake of low-nutrient, high-calorie foods with that of nutrient-dense, low-energy foods.<sup>9</sup>

Currently, there are only two pharmacologic options approved by the US Food and Drug Administration for long-term weight management - Sibutramine (Meridia) and Orlistat (Xenical).<sup>9</sup> In the nutrient inhibitor class, Orlistat (an inhibitor of gastrointestinal lipase) prevents the absorption of approximately 30% of the fat that is consumed and must be taken at the time of the fat consumption. Undesirable side effects such as flatulence and oil leakage in the stool often occur early in the course of treatment with this medication. Each of these weight loss medications is typically used as a single agent. The expected weight loss varies greatly but is typically 5% to 10% of initial weight.<sup>10</sup> In randomized clinical trials, orlistat in obese persons with T2 DM at baseline led to improved glycemic control and a weight reduction of 6% over 1 year versus 4% weight loss with placebo.<sup>11,12</sup>

A recently published meta-analysis concerning the efficacy of pharmacological agents for obesity reported that average weight loss was approximately four kilograms more than for placebo users and that no drug or class of drugs was clearly superior.<sup>13</sup> Many persons who do not respond to weight loss diet or medications are candidates for weight loss surgery if they are extremely obese (BMI >40 kg/m<sup>2</sup>) or if they have a BMI >35 to 40 kg/m<sup>2</sup> and one or more comorbid conditions, items that are typical elements of the MetS.

Other options for long-term weight management are surgical therapy or gastric bypass surgery. Several components of the MetS usually improve in concert with weight loss after surgery, including lipids and glucose levels, but assiduous follow-up is needed. Laparoscopic techniques that include putting a collar around the proximal end of the stomach are now available.

## **PHARMACOTHERAPY**

For patients whose risk factors are not reduced adequately by lifestyle changes, pharmacologic interventions to control their blood pressure and lipid levels are indicated. Aggressive pharmacologic management of risk factors has been shown to be more effective than routine care in preventing cardiovascular disease in patients with Type 2 Diabetes Mellitus.

### **Blood pressure**

Systolic BP of 130 mm Hg or higher and diastolic BP of 85 mm Hg or higher are criteria for MetS. There are currently no recommendations to introduce pharmacologic treatment until BP of  $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic is present. However, in patients with diabetes, treatment should be introduced at lower BPs ( $\geq 130$  mm Hg systolic or  $\geq 80$  mm Hg diastolic).

No particular antihypertensive agents has been identified as being preferable for hypertensive patients who also have MetS. Patient responses to individual pharmacological agents should be monitored, and factors other than the blood pressure response should be considered. While diuretic therapy is recommended to be part of the antihypertensive regimen, consideration should be given to the possibility that diuretics at high doses can increase insulin resistance and atherogenic dyslipidemia.<sup>14</sup> Beta blockers have also been shown to be related to weight gain and T2 DM in some population studies, but the long-term safety and efficacy of beta blockers and diuretics has

been effectively demonstrated in many clinical trials, including the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) that included >40,000 patients.<sup>15,16</sup>

Angiotensin receptor blockers or angiotensin converting enzyme inhibitors can also be considered, especially if diabetes is present, or if microalbuminuria or proteinuria is present or future concern. Whether treatment at lower levels in persons with MetS who do not have diabetes will reduce an important area of investigation.

Hypertension is both a defining characteristic of and a key cardiovascular risk factor in the metabolic syndrome. Early combination therapy for hypertension has become a more broadly accepted standard for patients with diabetes. Whether this approach to treatment is of potential benefit in those with the metabolic syndrome has not been carefully examined. Early use of either angiotensin-converting enzymes inhibitors or angiotensin II receptor blockers has been suggested for those with the metabolic syndrome. Results from a subgroup analysis of the Irbesartan/HCTZ Blood Pressure Reductions In Diverse Patient Populations (INCLUSIVE) trial were reported to determine the efficacy of fixed-dose combinations of irbesartan-HCTZ in patients with the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP).<sup>17</sup> Individuals with uncontrolled systolic blood pressure (SBP) were treated with forced titration to target SBP levels. A total of 386 (46%) of the study cohort of 844 patients met the criteria for the metabolic syndrome. Aggressive titration of irbesartan-HCTZ therapy reduced SBP by -21.0 mm Hg  $\pm$  14.3 mm Hg, with 73% of patients with the metabolic syndrome achieving an SBP of <140 mm Hg or <130 mm Hg for those with coexisting type 2 diabetes. Such studies support the use of both aggressive titration and early combination therapy for those with the metabolic syndrome with uncontrolled blood pressure.<sup>18</sup>

### Lipids

We've had substantial evolution in our treatment approach to lipids over the last few decades. Lipid-lowering drugs in patients with the metabolic syndrome are: statins, ezetimibe, and bile-acid sequestrants; other drugs that promote moderate reduction are nicotinic acid and fibrates, which are considered to be secondary drugs. (Table 2)

For dyslipidemia, the 10-year risks for ASCVD are defined by four risk categories of elevated LDL-C levels: high risk (> 20%), moderately high risk (10-20%

with two or more risk factors), moderate risk (< 10% with two or more risk factors), and lower risk (< 10% with 0 - 1 risk factor). Risk stratification is used for target LDL-C levels. If the triglyceride level is higher than 500 mg per dL, then lowering the triglyceride level to 500 mg per dL or less takes primacy over LDL-C lowering. After LDL-C and non HDL-C goals are achieved, a tertiary target is raising HDL-C level. No specific goals for raising HDL-C levels are specified.<sup>14</sup>

**Table 2.** Drugs affecting lipoprotein metabolism (adapted after Ref. 6).

Drug classes	Lipid / Lipoprotein effects	Potential side effects
Statins <sup>a</sup>	LDL $\downarrow$ 18%-55% HDL $\uparrow$ 5%-15% TG $\downarrow$ 7%-30%	Myopathy; increase liver enzymes
Bile acid sequestrants <sup>b</sup>	LDL $\downarrow$ 15%-30% HDL $\uparrow$ 3%-5% TG no change or increase	Gastrointestinal distress, constipation
Nicotinic acid <sup>c</sup>	LDL $\downarrow$ 5%-25% HDL $\uparrow$ 15%-35% TG $\downarrow$ 20%-50%	Flushing, hyperglycemia, hyperuricemia; upper GI distress
Fibric acids <sup>d</sup>	LDL $\downarrow$ 5%-20% (may be increased in patients with high TG) HDL $\uparrow$ 10%-20% TG $\downarrow$ 20%-50%	Dyspepsia; gallstones, myopathy; non CVD deaths in WHO study
Cholesterol absorption inhibitor (ezetimibe)	LDL $\downarrow$ 18% HDL $\uparrow$ 1% TG $\downarrow$ 8%	Gastrointestinal symptoms

- a. Lovastatin (20-80 mg/daily), pravastatin (20-40 mg/daily); simvastatin (20-80 mg/daily); fluvastatin (20-80 mg/daily); atorvastatin (10-80 mg/daily);  
b. Cholestyramine (4-6 g/daily), cholestipol (5-20 g/daily), colestevlam (2,6-3,8 g/daily);  
c. Immediate release (crystalline) nicotinic acid (1,5-3 g/daily), extended release nicotinic acid (1-2 g/daily) and sustained release nicotinic acid (1-2 g/daily);  
d. Gemfibrozil (600mg twice daily), fenofibrate (200mg daily), clofibrate (1000 mg twice daily).

### Statins

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial has shown that statins lower LDL cholesterol levels and reduce the incidence of mortality associated with CHD in patients with known CVD. Using a statin alone has been shown to decrease LDL cholesterol levels by 35% and to decrease very lowdensity lipoprotein (VLDL) levels by 39%.<sup>14</sup> Statins also lower the incidence of MI or stroke by more than 33% in patients with coronary artery disease (CAD). The greatest impact was shown in persons older than 75 years. The most recently approved drug in this class is rosuvastatin. In five multicenter open-label trials involving a total of 580 patients, treatment with low-dose rosuvastatin (10 mg

for 12 weeks significantly improved the lipid panel from baseline. Rosuvastatin lowered LDL-C and the non-HDL-C/HDL-C ratio by 47%, non-HDL-C by 43%, and triglycerides by 23% while increasing HDL-C by 10%). Low-dose rosuvastatin also raised apoA and lowered apoB levels.

### **Fibrates**

The Veterans Administration HDL Intervention Trial (VAHIT) found that gemfibrozil increased HDL cholesterol levels and decreased triglyceride levels by approximately 30%. This study also demonstrated that gemfibrozil can reduce death from CHD or nonfatal MI in patients who do not have high risk LDL cholesterol levels. The Diabetic Atherosclerosis Intervention Study (DAIS) looked at the effects of fenofibrate on persons with Type 2 DM and also reported increased HDL cholesterol and decreased triglyceride levels. The progression of CAD was also reduced in this cohort.

Statin-fibrate combination is attractive but the risk for side effects (myopathy) is higher.

### **Niacin**

Niacin, alone or in combination with statins, has been utilized in a number of studies involving patients with type 2 diabetes. In general, niacin increases HDL-C to the greatest extent of all available monotherapies: from 15% to 35% at higher daily doses on the order of 3 grams. Niacin lowers LDL levels more effectively than a statin, although not quite as well as a bile acid sequestrant. Hyperglycemia occurs in a modest number of niacin users, and approximately 10% to 30% of patients with diabetes will require adjustments in their hypoglycemic medications.

### **Insulin resistance**

A meta-analysis assessed the relationship between the metabolic syndrome, CVD, and new-onset diabetes. A total of 9 primary studies published between 2002 and 2004 that evaluated more than 50,000 patients were included in the review. The median follow-up time was approximately five years. The overall risk for CVD was two times greater in patients with the metabolic syndrome compared with those without, and the risk for new-onset diabetes was three times greater. This confirms the need to identify patients with the metabolic syndrome in order to make every effort to prevent the development of diabetes and CVD.

Nonpharmacologic intervention is appropriate as initial therapy for patients with impaired fasting glucose or impaired glucose tolerance, but insulin-sensitizing drugs may be considered an early treatment option if

lifestyle intervention is ineffective, even in the absence of overt diabetes.

The Diabetes Prevention Program showed success with the use of metformin, which can counteract insulin resistance by increasing insulin sensitivity and decreasing hepatic glucose production. Metformin can also delay or even prevent the development of Type 2 DM. These results were seen in men and women and in all races.<sup>26</sup>

Thiazolidinediones will improve glucose uptake by adipose tissue and skeletal muscle, leading to a decrease in insulin secretion. The Troglitazone in the Prevention of Diabetes (TRIPOD) study showed an arrest in the decline of  $\beta$ -cell function in women with prior gestational DM.<sup>27</sup> The Diabetes Prevention Program discontinued the arm of its study that included troglitazone in the prevention of Type 2 DM due to the drug's hepatotoxicity.

The thiazolidinediones are represented by pioglitazone and rosiglitazone. They can be used in the prevention and treatment of insulin resistance in the early stages of the metabolic syndrome.<sup>28</sup> They may also help with the dyslipidemia associated with metabolic syndrome. Pioglitazone increased adiponectin 3-fold and decreased hepatic fat content, while rosiglitazone increased adiponectin and decreased FFA and PAI-1 in Type 2 diabetes patients.<sup>29,30</sup> In a large study of 3,700 patients from 28 European countries, the effects of pioglitazone, metformin, and the sulfonylurea agent gliclazide on LDL particle size were studied. In monotherapy and combination therapy trials, pioglitazone demonstrated a favorable increase in LDL size.<sup>31</sup>

In the United States was conducted a trial which enrolled subjects with elevated fasting and postload plasma glucose levels. The study included three arms of therapy: lifestyle changes, metformin, and troglitazone. The troglitazone intervention was stopped early because of liver toxicity. In comparisons with placebo users, the persons who followed the lifestyle prescription experienced a 58% lower progression rate to T2 DM and the metformin users had a 31% lower development of T2 DM.<sup>32</sup>

Several agents currently in development hold promise in the treatment of insulin resistance, and, ultimately, cardiovascular disease. The dual PPAR-alpha/gamma agonists are currently the farthest along in development. Tesaglitazar was evaluated in a 12-week study in 390 nondiabetic subjects with insulin resistance.<sup>33</sup>

In a presentation by Jim McCormack, novel agents in development that may target insulin resistance at

more downstream points, such as direct tyrosine kinase activators, protein tyrosine phosphatase 1 B inhibitors, and inhibitors of 11 BHS-1, were discussed.<sup>34</sup> None of these agents are ready for prime time, but the hope is that targeting insulin resistance at more specific sites will lead to more efficacious treatment with fewer adverse effects.

### Prothrombotic state

Based on the efficacy of aspirin in reducing CVD events both in primary and secondary prevention, and the American Heart Association recommendations to consider aspirin therapy in those with a 10-year risk of CHD  $\geq 10\%$ , most patients with MetS would be suitable candidates for this drug.<sup>5</sup> Identification of those with a high CRP level ( $> 3$  mg/L) may be candidates for stratification to a higher risk category for more aggressive treatment, which would involve

intensifying lifestyle alterations, low aspirin, and lower LDL-C goals ( $<100$  mg/dL).<sup>14</sup>

In patients with atherosclerotic cardiovascular disease in whom aspirin is contraindicated, clopidogrel should be considered.

### Proinflammatory state

Both the proinflammatory and prothrombotic states of metabolic syndrome derive largely from the secretory activity of adipose tissue. Cytokines and other inflammatory markers or signaling molecules released by adipocytes - termed "adipokines"-include leptin, tumor necrosis factor alpha (TNF-alpha), interleukin-6, resistin, and adiponectin. Adiponectin levels are inversely related to fasting plasma insulin and glucose levels.<sup>38</sup> Weight loss by obese individuals has been associated with increased adiponectin levels.

Both the proinflammatory and prothrombotic

**Table 3.** Cardiovascular risk reducing treatment for persons with the metabolic syndrome (MetS) (adapted after Ref. 1).

Risk factor	Recommended treatment	Treatment and/or goal
Obesity	Moderate 500-1000 calorie/d reduction per Adult Treatment Panel III diet recommendations	Waist circumference $>35$ in for women and $>40$ in for men constitutes higher risk levels; suggested reduction of body weight by 7-10% over 6-12 months as needed
Physical inactivity	30 min/d of moderate intensive physical activity	Increasing amount may provide additional benefits
LDL cholesterol	Statins alone or in combination with nicotinic acid or a cholesterol absorption inhibitor	$<30$ mg/dl for most MetS patients( $<100$ mg/dl as an optional goal; $<100$ mg/dl for those at high ( $>20\%$ ) risk or with diabetes; $<70$ mg/dl for those with MetS accompanied by CVD or diabetes
HDL cholesterol	Nicotinic acid or fibrate	Minimal goal $\geq 40$ mg/dl in men and $\geq 50$ mg/dl in women; optimal $>60$ mg/dl
Tryglicerides	Nicotinic acid or fibrate	Minimal goal $<150$ mg/dl
Elevated blood pressure	Therapy dependent on presence of other conditions as recommended by JNC <sup>7</sup> ; high dose diuretic or betablocker may negatively impact insulin resistance or dyslipidemia	Minimal goal $<130$ mm Hg systolic and $<85$ mm Hg diastolic (or 130/80 mm Hg if diabetes is present)
Insulin resistance/ hyperglycemia	Lifestyle modification for all patients with MetS; insulin metformin, thiazolidinediones and other hypoglycemic medications as appropriate for those with diabetes; no hypoglycemic therapy indicated for MetS without diabetes	$<7$ Hemoglobin A1c for those with diabetes; $<100$ mg/dl fasting glucose for those with MetS (without diabetes)
Prothrombotic state	Low dose aspirin prophylaxis	Initiate therapy if subjects is at intermediate (10-20% 10 year risk) or high ( $>20\%$ with diabetes or CVD) risk
Proinflammatory state	Both aspirin and statins provide modest and variable reductions in CRP levels	CRP $>3$ mg/l indicates high risk; persons with these levels should be stratified to a higher risk level for more intensive treatment

states resulting from obesity may increase the risk of coronary events. CRP is a pivotal acute-phase reactant that is considered an index of inflammation and is associated with cardiovascular risk, particularly the risk of acute coronary syndrome. Within the nondiabetic population of the Insulin Resistance Atherosclerosis Study, the CRP level varied directly as a function of the number of metabolic abnormalities.<sup>35</sup>

CRP is associated with acute coronary syndrome through its ability to destabilize and rupture atherosclerotic plaque.<sup>36</sup> PAI-1 released in increased amounts from excess abdominal adipose tissue tends to increase the thrombotic consequences of plaque rupture. In a study of obese women, visceral fat and PAI-1 were significantly higher in patients with T2 DM (vs those without), and visceral fat mass was independently correlated with increased PAI-1 activity (ie, decreased fibrinolysis).<sup>37</sup>

### Prevention

The U.S. Preventive Services Task Force recommends intensive behavioral dietary counseling for adult patients with known risk factors for cardiovascular disease.<sup>24</sup> The evidence for counseling for physical activity is not yet strong enough to merit a recommendation.<sup>24</sup> Family physicians need to be more effective at helping patients adopt healthy lifestyle habits. The Diabetes Prevention Program demonstrated that vigorous lifestyle intervention in patients who are prediabetic could reduce the rate of developing diabetes by more than 50 percent (from 11 to 4.8 percent).<sup>25</sup>

A summary of specific treatment recommendations based on the discussion above is provided in Table 3.

### CONCLUSIONS

Because MetS is highly prevalent in middle-aged and older adults, it is urged that both primary care and subspecialty physicians assess their patients for MetS at regular intervals. Identification of MetS may accustom physicians to simultaneously treating multiple risk factors (particularly abdominal obesity, dyslipidemia, and elevated BP), instead of the traditional model of treating risk factors in isolation. Most importantly, intensified efforts at lifestyle therapy by trained individuals are needed if a significant impact is to be made on MetS and its complications.<sup>1</sup>

The metabolic syndrome is increasingly common, and the characteristic components of this disorder are obvious targets for treatment to reduce the risk of both diabetes and CVD. The exciting advances

in pharmacologic therapy for this syndrome raise the possibility that both nonpharmacologic and pharmacologic treatments will be increasingly applied to those at greatest risk. Only with these aggressive efforts can we hope to stem the tide of the metabolic syndrome and its inherent risk of T2 DM and CVD.

Future directions are to establish the value of treating atherogenic dyslipidemia beyond LDL-lowering therapy and the efficacy of treating insulin resistance for reducing the risk of CVD. Future randomized controlled trials should be conducted to evaluate the comparative benefits of different treatment approaches on hard endpoints (cardiovascular events, preventing type 2 diabetes) as well on surrogate endpoints (lipid levels, inflammatory markers, circulating thrombotic markers, glycemic regulation).

Challenges remaining in the identification of high-risk persons include the introduction of clinical markers of insulin resistance, integration of postchallenge glucose and lipid concentrations, and better definition of the role of inflammatory, prothrombotic, and genetic factors. Improved understanding of the risk factors for metabolic syndrome is required, and clinical trials of therapeutic interventions specifically targeted to this syndrome need to be conducted.

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