Cardiovascular Risk Factors in the Metabolic Syndrome: Impact of Insulin Resistance on Lipids, Hypertension, and the Development of Diabetes and Cardiac Events

Stuart W. Zarich, MD, FACC, FASE

Division of Cardiology, Department of Medicine, Bridgeport Hospital, Yale School of Medicine, Bridgeport, CT

Metabolic syndrome (MS) is associated with excess cardiovascular risk above and beyond the contribution of traditional risk factors. It is a proinflammatory and prothrombotic condition associated with underlying insulin resistance. Hypertension and hyperlipidemia in the setting of MS are also associated with excess cardiovascular risk, as is the development of new onset diabetes during the course of therapy. Although impaired fasting glucose and impaired glucose tolerance (IGT) both predict the development of diabetes mellitus, IGT more strongly predicts CV events because it is associated with a greater degree of insulin resistance. Early recognition and aggressive lifestyle interventions are the cornerstones of treatment, with aggressive pharmacologic therapy introduced when appropriate. It is expected that future studies will more clearly define the early use of insulin-sensitizing agents in MS.
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Key words: Metabolic syndrome • Diabetes mellitus • Hypertension • High-density lipoprotein cholesterol • Low-density lipoprotein cholesterol

Kylin[1] first described the association of hypertension (HTN), hyperglycemia, and gout in 1923. Later, the clustering of cardiovascular (CV) risk factors associated with insulin resistance was introduced as "syndrome X" by Reaven[2] and as the deadly quartet and dysmetabolic syndrome by others. In addition to obesity, HTN, glucose intolerance, high triglycerides, and

low high-density lipoprotein (HDL) cholesterol, other metabolic abnormalities have been associated with this syndrome including impaired fibrinolysis and a proinflammatory diathesis.[3,4] This syndrome is most commonly recognized today as metabolic syndrome (MS) and affects approximately 24% of the US adult population.[5] According to the Third National Health and Nutrition Examination Survey (NHANES III), MS affects nearly 50 million people, and utilizing the Third National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition, this includes 44% of subjects over the age of 50.[6] The major definitions for MS and insulin resistance in the United States are shown in Table 1.

Metabolic syndrome is closely associated with obesity, which has increased in prevalence in the United States and worldwide, creating an unprecedented risk for CV disease. Obesity is prevalent across all demographic groups and is not gender-specific. Nearly two thirds of all adult Americans are now considered overweight or obese. Obesity is also rampant in children and adolescents, with 50% of severely obese youth meeting MS criteria.[7] Pathologic studies have shown that obesity is associated with accelerated atherosclerosis in the young, with traditional risk factors accounting for only 15% of the effect.[8] It is now estimated that the lifetime risk of developing diabetes for children born in 2000 is 33% to 39%.[9]

Table 1
Metabolic Syndrome Definitions

ATP III Diagnostic Criteria for Metabolic Syndrome

Risk Factor	Cutpoint
Abdominal obesity	
Men	Waist circumference ≥ 40 in
Women	Waist circumference ≥ 35 in
Elevated triglycerides	≥ 150 mg/dL
Low HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Elevated blood pressure	≥ 130/≥ 85 mmHg
Elevated fasting glucose	≥ 110 mg/dL

AACE Diagnostic Criteria for the Insulin Resistance Syndrome

Risk Factor Component	Cutpoint for Abnormality
Overweight/obesity	BMI ≥ 25 kg/m^2
Elevated triglycerides	≥150 mg/dL
Low HDL	
Men	< 40 mg/dL
Women	< 50 mg/dL
Elevated blood pressure	≥ 130/85 mm Hg
2 h post-glucose challenge	
Other risk factors	Family history of Type 2 diabetes, hypertension, or cardiovascular disease
	Polycystic ovary syndrome
	Sedentary lifestyle
	Advancing age
	Ethnic group having high risk for Type 2 diabetes or cardiovascular disease

World Health Organization (WHO)

Definition contains measures of insulin resistance or impaired glucose tolerance and microalbuminuria.

ATP III, Third National Cholesterol Education Program Adult Treatment Panel III; HDL, high-density lipoprotein; AACE, American Association of Clinical Endocrinologists; BMI, body mass index.

Cardiovascular Risk in MS

Metabolic syndrome significantly increases the risk of CV disease, even in the absence of overt diabetes mellitus (DM).[10] In over 10,000 NHANES III participants, MS was associated with a 2-fold increased risk of myocardial infarction (MI) and stroke in both men and woman. The age-adjusted prevalence of CV disease was highest in NHANES subjects with both DM and MS (19.2%) and in those with MS in the absence of DM (13.9%), compared with those without either MS or DM. Interestingly, diabetes without MS was associated with a similar prevalence of CV disease (7.5%), compared with subjects without either MS or DM (8.7%).[6] The odds ratios for the prediction of CV events in MS were similar with diabetics excluded from analysis, indicating that MS is strongly predictive of CV events independent of hyperglycemia. The strongest association with CV events was seen with hypertriglyceridemia, especially in women. Low HDL cholesterol, HTN, and diabetes were also independent predictors of the prevalence of CV disease in older NHANES

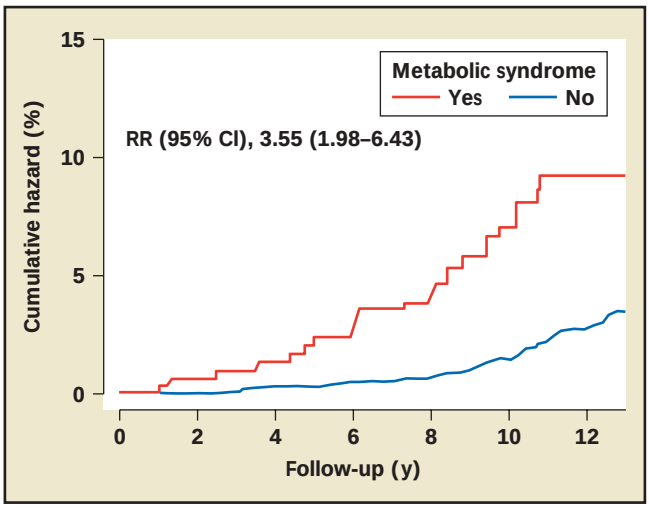

Figure 1. *Cardiovascular disease mortality increased in the metabolic syndrome. RR, relative risk; CI, confidence interval. Reprinted with permission from Lakka HM et al.*[12]

participants, whereas hyperglycemia was an independent predictor in the entire NHANES III cohort.

In the Botina Study,[11] MS was associated with a 3-fold increase in MI and stroke in Finnish subjects 35 to 70 years old with a family history of Type 2 DM. However, CV disease and DM were present at baseline in one third of the patients. In the Kuopio Ischaemic Heart Disease Risk Factor Study,[12] 1209 previously healthy men without CV disease or DM were followed prospectively for 11.6 years. MS was associated with a 3-fold risk of CV death after adjustment of conventional risk factors regardless of the MS definition used (Figure 1). In recent analyses of the West of Scotland Coronary Prevention Study[13] (WOSCOPS), the Scandinavian Simvastatin Survival Study (4S), and the Air Force/Texas Coronary Atherosclerosis Prevention Study,[14] MS (after excluding DM) was associated with a 1.3- to 1.5-fold increase in CV events adjusting for conventional risk factors. Of the components of MS, low HDL cholesterol was the most common factor independently associated with CV events.

It has been well documented that the risk of CV disease is elevated prior to the clinical diagnosis of Type 2 DM. Insulin-resistant prediabetic subjects in the San Antonio Heart Study[15] (SAHS) had lower HDL levels and higher systolic blood pressure and triglyceride levels compared with subjects who did not develop DM, leading to the "ticking-clock" hypothesis.[16] In the Nurse Health Study,[17] women who developed DM during follow-up had a 3.8-fold increased risk of MI prior to their diagnosis of DM and a 4.6-fold relative CV risk for the period after the diagnosis of DM (Figure 2).

The increased CV risk in MS appears to exceed the cumulative risk of the sum of its individual components. In the Prospective Cardiovascular Munster Study,[18] MI risk was increased 2.5-fold in the presence of DM or HTN, 8-fold with both DM and HTN, and nearly 20-fold with DM, HTN, and hyperlipidemia. MS was associated with increased CV events, irrespective of the Framingham Risk Score (FRS). Adding measurements of C-reactive protein (CRP) enhanced the predictive model for CV events. Most men with MS are considered only at intermediate risk (FRS 10% to 20%) despite their known high risk of CV events. Although the FRS may underestimate CV risk in MS (as the FRS does not include measurements of obesity, triglycerides, insulin resistance, or novel risk factors), it has been suggested that a global risk between 15% to 20% in the presence of MS might be considered CV risk equivalent.[19] Because ATP III does not specify whether subjects with MS should receive more intensive therapy for underlying disorders, recent guidelines suggest that MS patients with established CV disease are at very high risk and warrant consideration to treat to a low-density lipoprotein (LDL) cholesterol target of 70 mg/dL.[20]

If a major use of the MS criteria is to identify patients with insulin

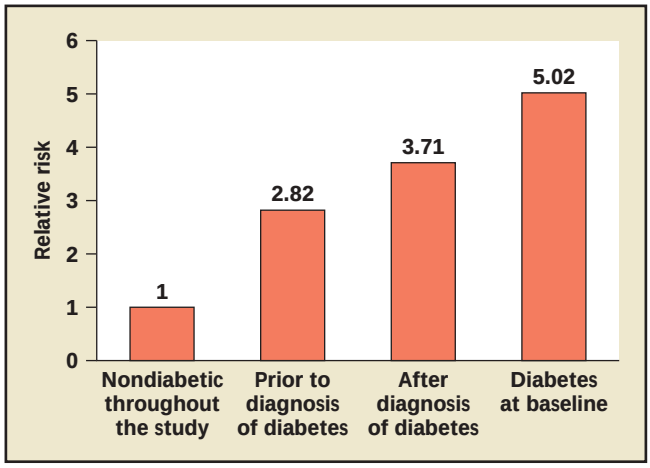

Figure 2. *Elevated risk of cardiovascular disease prior to clinical diagnosis of Type 2 diabetes. Reprinted with permission from Hu FB et al.*[17]

resistance and a clustering of CV risk factors and increased CV risk, it is important to realize that a substantial number of at-risk individuals with insulin resistance do not meet ATP III criteria for MS. A recent study in 74 healthy, non-diabetic subjects found that only 12% met ATP III criteria for MS.[21] A euglycemic clamp method showed that an additional 30% of subjects without MS were insulin resistant. Insulin-resistant subjects without MS had higher glucose, very low-density lipoproteins (VLDLs), triglyceride, small dense low-density lipoprotein (sd-LDL), and total LDL levels, and lower HDL levels than insulin-sensitive subjects. Similarly in the Bruneck Study,[22] insulin resistance was present in 88% of subjects with low HDL and in 84% of subjects with high triglyceride levels. McLaughlin and colleagues[23] have shown that 3 easy-to-obtain metabolic markers can identify overweight, insulin-resistant subjects at increased CV risk: triglycerides greater than 130mg/dL, a triglyceride/HDL ratio of 3.0 or higher, and a fasting insulin level greater than 109 pmol/L.

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MS and the Development of Diabetes

In WOSCOPS, MS was a more striking predictor of DM (odds ratio 3.5) than of CV events. Men with 4 or 5 features of MS had a 3.7-fold increased risk of CV events and a 24.5-fold increased risk of DM. The ability of MS to predict DM was also examined in the SAHS.[24] Both the ATP III and modified World Health Organization criteria predicted the development of DM with a sensitivity of 43% to 53%. Impaired glucose tolerance (IGT) had a higher positive predictive value, whereas the combination of IGT and MS increased the sensitivity to 70%. MS by the ATP III criteria was associated with a 3.3-fold increased risk of DM, independent of IGT and fasting insulin levels. The ATP III criteria performed better in the prediction of DM with an impaired fasting glucose (IFG) definition of greater than 100mg/dL. Incorporating IGT into the MS definition may enhance the predictive ability for DM.[25]

The prevalence of CV disease is higher in subjects with IGT compared with those with normal glucose tolerance.[26-29] Impaired fasting glucose, however, appears to be a more heterogeneous disease with up to one third of subjects having normal glucose tolerance. In the Funagata Diabetes Study,[27] IGT doubled the risk of CV deaths, whereas IFG did not increase CV death compared with normal fasting glucose. Similarly, data from 5 Finnish cohorts showed that CV mortality in IGT was similar to newly diagnosed DM, which was worse than for IFG. Impaired glucose tolerance was predictive of CV events and CV mortality, independent of other CV risk factors.[28] Recently IGT was found to be an independent risk factor for CV mortality, independent of the development of overt DM.[29] Thus, although IFG and IGT both strongly predict the development of DM, IGT more strongly predicts CV events because it is associated with a greater degree of insulin resistance.[30] Interestingly, as the prevalence of IFG is low (2.2%), the overall contribution of global IFG to MS in the ATP III definition is low. Less than 20% of patients with MS in the Framingham population have IFG. Conversely, 26% of NHANES subjects with a normal fasting glucose had MS.

Central Role of Insulin Resistance in Accelerated CV Risk

Potential factors contributing to the pathogenesis of accelerated CV disease in MS are depicted in Table 2. The central components of CV risk in MS are visceral obesity and resultant insulin resistance. Although obesity is a powerful risk factor for DM and CV disease, substantial heterogeneity exists in the distribution of fat and the relationship between metabolic disturbances and obesity. A significant minority of obese subjects is not insulin resistant and, conversely, lean subjects may be insulin resistant. The prevalence of coronary artery disease in overweight and obese women without MS is similar to lean subjects without metabolic abnormalities, whereas dysmetabolic, lean subjects have a risk comparable to obese subjects with MS (Table 3).[31] Insulin resistance remains an independent predictor of atherosclerosis after correction for CRP and MS features.[32] Abdominal obesity (as measured by waist circumference or hip to waist ratio) is the form of obesity most strongly associated with insulin resistance and MS. Lipolysis is accelerated in visceral fat resulting in an increase in circulating free fatty acids (FFA), which adversely affects insulin action and glucose uptake (lipotoxicity) and increases hepatic VLDL production.[33,34]

Adipocytes secrete multiple proinflammatory cytokines, such as interleukin-6 (IL-6) or tumor necrosis factor alpha (TNF-alpha), and it is well appreciated that MS is a proinflammatory condition. Adipocytes

Table 2
Potential Abnormalities Associated with Atherogenesis in Metabolic Syndrome and Insulin Resistance

Visceral adiposity
Elevated FFA (lipotoxicity)
Adipokine production (adiponectin, leptin, resistin)
Impaired glucose tolerance
Diabetes mellitus
Impaired fasting glucose
Atherogenic dyslipidemia
↑ Triglycerides
↓ HDL
↓ LDL-particle diameter
Hemodynamic
↑ Blood pressure (≈50% of patients with hypertension are insulin resistant)
↑ Arterial stiffness
↑ Carotid intimal-medial thickness
Hemostatic
↑ Plasminogen activator inhibitor –1
↑ Fibrinogen, von Willebrand factor, thrombin
↑ Platelet aggregation
Proinflammatory diathesis
Elevated hs-CRP
Adipocyte-derived cytokines (IL-6, TNF-alpha)
Oxidative state
Endothelial dysfunction
↑ Mononuclear cell adhesion
↑ Cellular adhesion molecules
↑ Asymmetric dimethyl arginine
↓ Endothelial-dependent vasodilation

FFA, free fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; TNF, tumor necrosis factor.

also secrete and influence the actions of multiple signaling molecules ("adipokines") such as leptin, resistin, and adiponectin, which contribute to insulin resistance and diminished arterial compliance. Adiponectin levels are inversely correlated with insulin resistance and coronary artery disease.[35] Recently, an abnormal adiponectin gene mutation was noted in subjects with MS and was associated with diminished levels of adiponectin and increased CV risk.

It has been estimated that 30% of IL-6 production comes from adipocytes and directly influences the hepatic production of CRP. In the Insulin Resistance Atherosclerosis Study[36] (IRAS) and Women's Health Study[37] (WHS), CRP levels varied in direct proportion to the number of metabolic abnormalities. Chronic subclinical inflammation is an important part of MS, as CRP is independently related to obesity, insulin sensitivity, and MS itself. In fact, a compelling argument can be made for the addition of CRP to the MS definition.[36] The potential molecular mechanisms linking inflammation and insulin resistance have been recently reviewed by Ridker and associates.[38] For instance, TNF-alpha may impair insulin sensitivity by inhibiting insulin-mediated phosphorylation of the insulin receptor and thus reduces translocation of glucose type 4 transporters to the cell surface.

C-reactive protein remains a highly significant predictor of both DM and CV events when adjusted for other CV risk factors. In addition to correlating well with all 5 of the easily measured components of the ATP III definition of MS, CRP also correlates with insulin resistance, endothelial dysfunction, and impaired fibrinolysis. In the WHS, an elevated CRP level had almost an identical CV prognostication as MS, and added to the predictive value of MS.[37] Metabolic syndrome, coupled with the highest levels of CRP, was associated with a 2-fold greater risk of CV events when compared to MS subjects with the lowest CRP levels.

C-reactive protein may be directly associated with CV events through the ability to destabilize and rupture vulnerable atherosclerotic plaque. C-reactive protein increases plasminogen activator inhibitor-1 (PAI-1) expression in endothelial cells, which, in conjunction with PAI-1 released from visceral adipocytes, increases the thrombotic consequences of plaque rupture. Visceral fat mass independently correlates with PAI-1 levels and adjustment for PAI-1 levels attenuates the increased CV risk of MS.[39] Thus, impaired fibrinolysis in MS contributes to enhanced CV risk beyond traditional risk factors and the prevalence of atherosclerosis.

Although the role of environmental factors (high caloric density diet and sedentary lifestyle) appears to be the dominant factor in the epidemic of obesity and MS, the search continues to define genetic abnormalities associated with MS.[40] In addition to abnormalities in the adiponectin gene, several other candidate genes have been proposed.

Table 3
Relationship Between BMI, Metabolic Status, and Prevalence of Significant Angiographic CAD

BMI Status*	Metabolic Status**	n	Prevalence of CAD, %	Unadjusted OR	Adjusted OR***	95% CI	P
Normal	Normal	131	29.0	1.0	1.0	…	…
Normal	Dysmetabolic	50	56.0	3.12	3.11	1.50–6.41	0.002
Overweight	Normal	120	25.0	0.82	1.04	0.58–1.89	0.87
Overweight	Dysmetabolic	148	52.0	2.65	2.63	1.54–4.50	0.0004
Obese	Normal	75	17.3	.051	0.66	0.31–1.39	0.27
Obese	Dysmetabolic	247	42.1	1.78	1.91	1.17–3.14	0.01

*Normal BMI status indicated BMI ≤ 24.9; overweight, BMI to ≤ 29.9; obese, BMI ≥ 30.
**Dysmetabolic indicates metabolic syndrome or diabetes.
***Adjusted for age, race, menopausal status, and physical activity; 15 cases were excluded because of missing covariate data.
BMI, body mass index; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.
Reprinted with permission from Kip KE et al.[31]

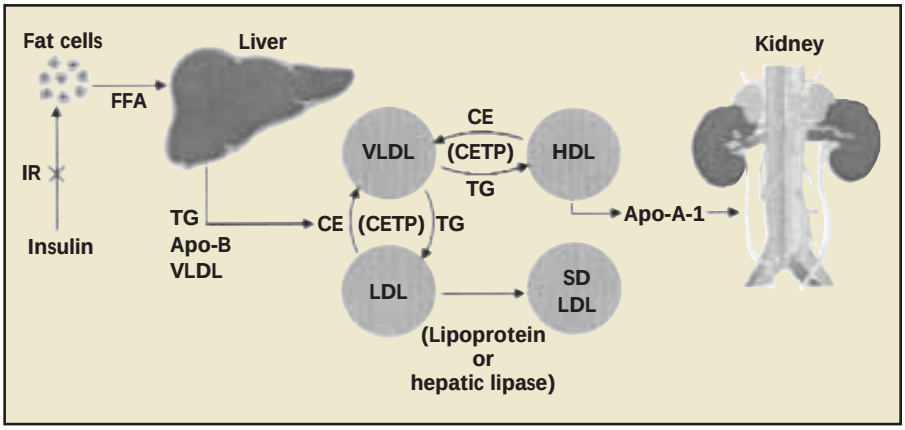
Peroxisome proliferators-activated receptor (PPAR)-gamma, leptin, and lipoprotein lipase gene regulation may also play a major role in the development of MS. No single gene has yet to be assigned the dominant role and it is likely that MS has a polygenic influence that requires activation by environmental factors. Finally, a link has been proposed for a common genetic basis for CV disease and insulin resistance ("thrifty gene" hypothesis).

Atherogenic Dyslipidemia

The lipoprotein abnormalities of MS consist of increased levels of triglycerides, apolipoprotein B (Apo-B), and sd-LDL, with marked reductions in HDL (including HDL-2) and apolipoprotein-A-1 (Apo-A-1).[41] Insulin resistance at the level of the fat cell increases intracellular hydrolysis of triglycerides and resultant FFA liberation, while also decreasing FFA uptake by the adipocyte (Figure 3).[42] Increased hepatic influx of FFAs increases VLDL secretion with insulin-resistant subjects having a 2- to 3-fold increase in VLDL levels compared with insulin-sensitive subjects. Hypertriglyceridemia leads to low HDL levels and increased sd-LDL particles, primarily due to the activity of cholesterol ester transfer protein (CETP). Triglyceride-rich HDL is hydrolyzed by hepatic lipase, and to a lesser extent lipoprotein lipase, which generates smaller HDL particles. Small dense HDL particles shed Apo-A-1, which is then catabolized in the kidney. Similarly, VLDL triglyceride is exchanged for LDL cholesterol in the presence of CETP. The hydrolysis of LDL triglyceride generates sd-LDL particles.

Insulin resistance is also associated with an increase in other triglyceride-rich lipoproteins such as remnant-like lipoproteins, which are independently associated with CV

Figure 3. *A simplified model relating insulin resistance (IR) to dyslipidemia and cardiovascular disease. Insulin resistance at the adipocyte results in increased release of fatty acids into the circulation. A similar accumulation of fatty acids could arise from defects in fatty acid transporters or intracellular binding proteins. Increased FFA flux to the liver stimulates the assembly and secretion of VLDL resulting in hypertriglyceridemia. In addition, VLDL stimulates the exchange of cholesterol esters from both HDL and LDL for VLDL TG. Apo-A-1 can dissociate from TG-enriched HDL. This free apo-A-1 is cleared from plasma, in part by excretion through the kidney, thus reducing the availability of HDL for reverse cholesterol transport. TG-enriched LDL can undergo lipolysis and become smaller and denser. Low levels of HDL and the presence of small dense LDL are each independent risk factors for cardiovascular disease. FFA, free fatty acids; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; Apo-A-1, apolipoprotein-A-1; Apo-B, apolipoprotein-B; CE, cholesterol ester; CETP, CE transfer protein; SD, small dense. Reprinted with permission from Ginsberg H.*[42]



disease.[43] To capture the risk of triglyceride remnants the calculation of non-HDL cholesterol according to ATP III guidelines can be performed when triglycerides exceed 200 mg/dL. Remnants may be atherogenic by impairing endothelial vasodilatation and activating adhesion molecules and platelet aggregation. Some of the atherogenicity of triglyceride-rich lipoproteins may be derived by the near universal occurrence of increased VLDL levels with low HDL and increased sd-LDL (lipid triad), which is characteristic of insulin resistance. However, recent prospective data and meta-analysis suggest that triglyceride levels are independent predictors of CV disease.[44] Statins lower remnant particles, which may contribute to their cardioprotective effect.

Prospective case control trials have shown that sd-LDL is associated with an increased CV risk. In the Quebec Cardiovascular Study,[45] sd-LDL was associated with a 2.2-fold increase of CV disease, independent of LDL, Apo-B, triglyceride, and HDL levels. Subjects with increased insulin levels in combination with elevated Apo-B levels and a small, dense pattern were at particularly high risk (> 10-fold compared with subjects with normal insulin and Apo-B levels). Optimization of glycemic control by insulin and thiazolidinediones (TZDs) increases LDL particle size, as does treatment with niacin. Statins markedly reduce total LDL concentrations, but in general do not alter particle size distribution. Fibrate therapy typically increases particle size, but clinical data are conflicting.

Extended-release niacin has salutary effects on all 3 components of atherogenic dyslipidemia (raising HDL and lowering triglycerides and sd-LDL). High-dose niacin may increase insulin resistance; thus, lower doses of niacin may be prudent in MS subjects (≤ 2 g/day). Combination therapy with simvastatin and niacin resulted in marked clinical and angiographic improvement in subjects with low HDL levels.[46] MS subjects also showed significant benefit with combination therapy. The protective increase in HDL-2 may be attenuated by the use of antioxidant vitamins.

Fibric acid derivatives reduce VLDL output, enhance catabolism of triglyceride-rich particles, upregulate Apo-A-1 gene expression, raise HDL, and reduce gene expression for PAI-1 and fibrinogen. Fibrates also increase lipoprotein lipase activity, which may reduce sd-LDL and stimulate FFA uptake and catabolism. Fibrate therapy has been effective in both primary and secondary prevention studies.[47] Gemfibrozil therapy was most beneficial in those who were overweight or those with elevated fasting insulin levels, suggesting that fibrate therapy may be particularly beneficial in MS. By multivariate analysis, HDL levels on treatment inversely correlated with CV events, but LDL and triglyceride levels were not predictive. Of interest, HDL-2 and Apo-A-1 concentrations were not affected by gemfibrozil therapy. Similarly, fenofibrate has been shown to slow the progression of coronary artery disease in DM subjects.[48] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial[49] evaluated the ability of this fibric acid derivative to reduce cardiovascular events. Diabetic patients were randomized to either 200 mg daily of micronized fenofibrate or placebo if they had baseline total cholesterol (TC) between 115-250 mg/dL and either a TC/HDL-C ratio of 4.0 or more or a plasma triglyceride level of 88-442 mg/dL. At 5-year follow-up, the primary endpoint of CHD death/nonfatal MI was non-significantly reduced by 11% ($P = .16$) in the fenofibrate group. Nonfatal MI was significantly reduced by 24% ($P = .010$). However, CHD death was non-significantly increased by 19% ($P = .22$). Complicating efforts to evaluate the benefit of fenofibrate in this trial was the increased use of statins in the placebo group, which may have contributed to decreased event rates. Further clarification of the effects of fibric acid derivatives is warranted but their use may be limited to those patients in whom triglyceride reduction therapy is indicated. It does not seem that they can replace statin therapy in diabetic patients.

Although bezafibrate therapy did not reduce CV events in a secondary prevention trial, the subgroup of patients with elevated triglyceride levels had a 40% reduction in CV events.[50] Recently bezafibrate was also shown to reduce the incidence of DM in high risk patients.[51] These results should not be generalized to other fibrates as bezafibrate may possess weak activity in PPAR-gamma, as well as PPAR-alpha, receptors.

Statin therapy is extremely effective in reducing CV events in patients with low HDL levels, IFG, and DM.[52-54] In the 4S trial, patients with high triglyceride and low HDL levels, in conjunction with elevated LDL lipids, had more characteristics of MS and a greater response to simvastatin compared with subjects with isolated elevated LDL levels.[52] Diabetics and those with IFG responded particularly well to simvastatin. Analysis of pooled data from 2 pravastatin trials of patients with low LDL levels showed that HDL and triglyceride levels were stronger predictors of CV events than in subjects with elevated LDL levels.[53] Diabetics with low HDL responded particularly well to pravastatin (34% reduction of CV event rates) compared with non-diabetics. Atorvastatin at both low and high dose significantly reduced triglyc-

eride levels and LDL, raising HDL in Type 2 diabetics as well. The addition of fenofibrate to atorvastatin was highly effective in patients with combined dyslipidemia.[54] Fenofibrate does not interfere with the glucuronidation of statins and may be a safer choice for combination therapy than gemfibrozil. A recent large trial of diabetic subjects with low LDL levels was stopped prematurely by the Data Safety Monitoring Board due to a marked reduction in CV events with low-dose atorvastatin.[55] Pravastatin therapy has been associated with a reduced incidence of new onset DM in a high-risk population, but this finding has not been confirmed in other statin trials.[56]

Rosiglitazone alone or with statin therapy has been shown to be both safe and effective in Type 2 DM.[56] The major effect of rosiglitazone on lipids was to increase HDL (predominantly cardioprotective HDL-2) and shift LDL to a large buoyant phenotype. Although LDL levels increased modestly, there was no significant increase in Apo-B levels. The addition of atorvastatin resulted in further increases in HDL levels and marked reductions in LDL and triglyceride levels. Combination therapy had no adverse effect on glucose metabolism or hepatic or muscle toxicity. Thiazolidinediones also reduced CRP and cytokine levels, as well as improved endothelial function. Pioglitazone, an agonist of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma) reduced the risk of recurrent MI by 28%, according to new results from the PROspective PioglitAzone Clinical Trial In MacroVascular Events Study (PROactive)[57] reported at the American Heart Association's 2005 Scientific Session. This is the first clinical data showing that a specific treatment for hyperglycemia can lead to a reduction in cardiac events.

Recently the ATP III panel released an update based on the latest clinical trials.[20] Patients with established CV disease and multiple risk factors of MS (especially elevated triglycerides, non-HDL cholesterol, and low HDL) are considered very high risk, which favors treatment to an LDL goal of less than 70 mg/dL. With moderate risk (FRS 10% to 20%) and an LDL 100 to 129 mg/dL, initiation of drug therapy is now considered an option. A more definitive study of statin therapy in patients with low LDL and elevated CRP levels is now underway and is projected to contain a large number of subjects with MS.[58]

Prognostic Value of MS in Hypertension

Hypertension is present in approximately 80% of patients with MS. Prospective follow-up of 1742 hypertensive patients without known CV disease for up to 10.5 years revealed that the presence of MS was associated with a near doubling of CV risk.[59] MS was an independent predictor of CV events in hypertensive patients, even after the exclusion of diabetic patients (relative risk of 1.43 compared with those with HTN without MS).

Insulin resistance was also an independent risk factor for CV events in the IRAS study and is known to increase oxidative stress, impair endothelial and microvascular function, and is associated with increased vascular stiffness. Metabolic syndrome was strongly associated with arterial stiffness and carotid intimal-medial thickness, independent of each of the individual components of MS.[60] Similarly impaired glucose metabolism was associated with increased central and peripheral arterial stiffness independent of conventional risk factors.[61] Hyperglycemia and hyperinsulinemia explained only 30% of the arterial changes in glucose-intolerant subjects, which occurred prior to the development of DM.

Recent evidence supports the concept of HTN as an inflammatory disease. Sesso and associates[62] showed that elevated CRP levels were associated with the development of new onset HTN and may share a common pathogenesis with the development of DM and atherosclerosis. C-reactive protein may promote arterial inflammation via direct or indirect interaction with the endothelium through diminished nitric oxide formation, enhanced vasoconstriction, platelet aggregation, PAI-1 expression and adhesion molecule expression, and up-regulation of angiotensin receptors. Metabolic syndrome is also associated with over a 2-fold increased risk of chronic renal disease and a 34% increase in microalbuminuria compared with controls.[63] Microalbuminuria in itself is associated with a doubling of CV risk and mortality, independent of traditional CV risk factors.[64]

Hypertension is associated with an approximate 2% per year incidence of the development of new onset DM, which appears to be independently associated with CV events.[65] In up to 16 years of prospective follow-up, 50% of previously untreated hypertensive subjects who went on to develop DM during pharmacologic treatment had IFG prior to treatment. Patients with new onset DM had a CV event rate nearly 3-fold higher than subjects who remained without diabetes throughout treatment (Figure 4), which was similar to patients with DM at the beginning of the study. New onset DM was not a predictor of CV events in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[66] but this surprising finding may be explained by the short follow-up (approximately 2 years) of patients after the development of DM

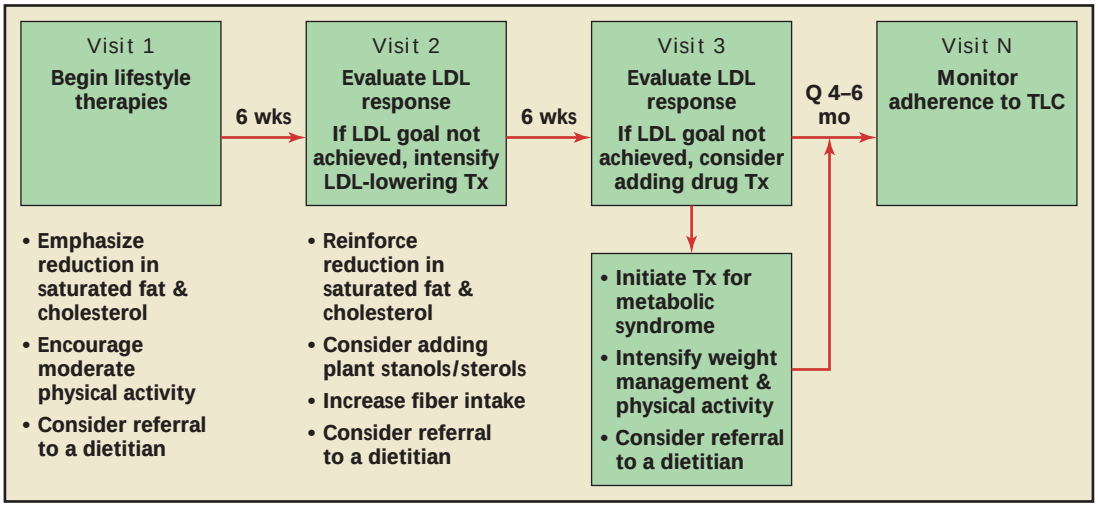


Figure 4. *A model of steps in therapeutic lifestyle changes (TLC). LDL, low-density lipoprotein; Tx, treatment. Reprinted with permission from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.*[76]

in that study. Over 50% of patients with IFG receiving diuretics in ALLHAT developed DM in 5 years of follow-up.

The findings of 11 prospective randomized trials of high-risk patients regarding the development of DM and CV medications were recently summarized by Pepine and Cooper-DeHoff.[67] Treatment with angiotensin receptor antagonists (ARBs), angiotensin receptor inhibitors (ACE-Is), and calcium channel blockers (CCBs) was associated with a lower incidence of DM compared with β-blockers and diuretics. The incidence of new onset DM with CCBs was intermediate between that of ARBs or ACE-Is and diuretics. ARBs and CCBs may also be superior to diuretic and β-blocker therapy in the prevention of stroke.[68] Although β-blockers uniformly worsened insulin sensitivity, the addition of α-blockade appeared to improve insulin sensitivity. In the Carvedilol or Metoprolol European Trial,[69] carvedilol was associated with a 22% lower incidence of new onset DM compared with metoprolol in heart failure patients. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Tartrate Comparison in Hypertensives (GEMINI) Trial[70] showed the ability of carvedilol to improve insulin resistance, reduce progression to microalbuminuria, and maintain glycemic control when compared to metoprolol tartrate.

Although current guidelines do not deal specifically with the choice of initial therapy in hypertensive subjects with MS, recent data suggest the use of ACE-Is or ARBs for MS patients with impaired glucose metabolism or microalbuminuria. There may also be a rationale for ARB/ACE-I combinations in hypertensive patients with glucose intolerance.[71]

This does not mean that β-blocker or diuretic therapy does not remain important in hypertensive subjects with MS. Unfortunately, blood pressure control with a systolic pressure below 140 mmHg is seen in less than 50% of treated hypertensive subjects.[72] Aggressive combination therapy is warranted to achieve targets, and should be considered in all patients with systolic blood pressures greater than 20 mmHg above goal. A recent clinical trial tested the approach from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (initiation of combination ARB/diuretic compared with ACE-I monotherapy) in diabetic subjects and found superior blood pressure control at 4 to 8 weeks with combination therapy.[73]

Early attainment of blood pressure goals appears to have prognostic importance. Although amlodipine and valsartan were found to be equivalent in the prevention of CV events in a high-risk hypertensive cohort, there was an increased risk of MI and a trend for increased stroke with valsartan. The excess CV risk with valsartan appeared in the first several months of therapy when systolic blood pressure was 4 to 5 mmHg higher than the amlodipine group.[74] As amlodipine appears to be equally effective as ACE-Is or ARBs in preventing CV events and does not increase insulin resistance, its use in MS seems appropriate. Aldosterone antagonists do not adversely affect glucose metabolism, are effective in reducing proteinuria and regressing left ventricular hypertrophy, and are particularly successfully in resistant hypertension.[75]

Importance of Early Recognition

Given the markedly increased risk in the general population of developing DM and resultant CV events, early

recognition of metabolic abnormalities and efforts at primary prevention are of paramount importance. Lifestyle modifications remain the cornerstone of therapy (Figure 4) and should be combined with aggressive pharmacologic control of metabolic factors when warranted.[76] A multifactorial intervention involving lifestyle modifications and aggressive pharmacologic therapy in high-risk diabetic patients with microalbuminuria was associated with a 50% lower risk of CV disease compared with conventional treatment of modifiable risk factors.[77] An aggressive approach appears to be similarly warranted in high-risk MS subjects.

Weight loss, dietary modification, and exercise form the foundation for lifestyle interventions in MS. Weight loss through diet and exercise, but not liposuction, reduces inflammatory markers in obese patients.[78] Several recent reviews emphasize the role of lifestyle interventions in MS and the prevention of DM.[79] Modest weight loss and regular exercise reduced the risk of developing DM by 50%, which is better than the results achieved with metformin in glucose-intolerant patients.[80] Alpha-glucosidase inhibitors, TZDs, and orlistat also appeared to retard the development of DM in high-risk subjects, which may result in improved CV outcomes. Bariatric surgery can also markedly improve glucose metabolism in obese subjects and may be appropriate in selected subjects.

The exact nature of diet therapy for MS subjects remains controversial. Subjects with MS may be placed on low-fat, high-carbohydrate diets, which may accentuate hyperinsulinemia and worsen components of the atherogenic dyslipidemia.[81] Although the role of substituting unsaturated fat for carbohydrates in MS is unclear at present, saturated and trans fats should be avoided. Similarly, simple sugars and refined foods should be limited with an emphasis on a high-fiber diet including complex carbohydrates from fruits and vegetables. High levels of dietary, advanced glycosylated end-products may enhance the toxicity of LDL via an enhanced oxidative state. Weight reduction is a major goal in MS and diet recommendations should include modest caloric restriction (500 to 1000 kcal/d) with realistic weight loss goals (7% to 10% over a 6- to 12-month period).[82] The Dietary Approaches to Stop Hypertension (DASH) program[83] emphasized the consumption of more fruits and vegetables and low-fat dairy products than ATP III and was designed specifically to combat hypertension. However, the presence of obesity and inflammation appears to modify the response to the DASH diet, as an elevated CRP level was associated with a blunted LDL and total cholesterol response, as well as higher triglyceride levels compared with subjects without an elevated CRP.

Conclusions

Metabolic syndrome is associated with an increased risk of CV beyond the contribution of its individual metabolic components. Visceral adiposity and associated insulin resistance are associated with a proinflammatory and prothrombotic state, as well as the release of adipokines, which may both directly

Main Points

- The clustering of cardiovascular (CV) risk factors associated with insulin resistance including obesity, hypertension, and glucose intolerance is most commonly referred to as metabolic syndrome (MS) and affects approximately 24% of the US adult population.
- Metabolic syndrome significantly increases the risk of CV disease, even in the absence of overt diabetes mellitus (DM), exceeding the cumulative risk of the sum of its individual components.
- Although impaired fasting glucose and impaired glucose tolerance (IGT) both predict the development of DM, IGT more strongly predicts CV events because it is associated with a greater degree of insulin resistance. Incorporating IGT in the MS definition may enhance the predictive ability for DM.
- The central components of CV risk in MS are visceral obesity and resultant insulin resistance. Insulin resistance remains an independent predictor of atherosclerosis after correction for C-reactive protein and MS features.
- Metabolic syndrome is an independent predictor of CV events in hypertensive patients, even after the exclusion of diabetic patients. Furthermore, hypertension may share a common pathogenesis with the development of DM and atherosclerosis.
- Early recognition of metabolic abnormalities and efforts at primary intervention are imperative. Lifestyle modifications remain the cornerstone of therapy and should be combined with aggressive pharmacologic control of metabolic factors when warranted.

and indirectly influence atherogenesis. Hypertension and hyperlipidemia in the presence of MS greatly enhances CV risk. However, current guidelines frequently underestimate CV risk in subjects with MS and may result in less than optimal treatment of CV risk factors.

Metabolic syndrome is also associated with a markedly increased risk of the development of DM, especially in the presence of impaired glucose metabolism. The development of DM in a patient being treated for hypertension appears to portend an increased risk of CV events comparable to subjects with hypertension and established DM. Identification of metabolic risk factors and aggressive lifestyle interventions are warranted in all patients, introducing aggressive pharmacologic intervention when appropriate. Current treatment should involve strategies known to improve insulin sensitivity. Future studies, including the Diabetes Reduction Approaches with Medication (DREAM) trial and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, are assessing the role of early intervention with insulin sensitizers (ie, TZDs, ACE-Is, ARBs) in the prevention of DM and CV events in high-risk individuals. ■

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