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# The Metabolic Syndrome: Inflammation and Endothelial Dysfunction

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The prevalence of obesity in both adults and children in the United States has increased significantly over the past 50 years. The metabolic syndrome is linked to obesity and a cluster of risk factors for atherosclerosis such as hypertension, dyslipidemia, and glucose intolerance.[1,2] Significant components of the pathogenesis of the metabolic syndrome include insulin resistance, endothelial dysfunction, and a proinflammatory and prothrombotic state in the vasculature.

Reaven[3] originally described the metabolic syndrome as the metabolic effects of insulin resistance in human disease, postulating that insulin resistance is associated with evidence of subclinical inflammation, impaired fibrinolysis, and hyperuricemia. These factors may result in an elevated risk of disorders such as diabetes mellitus and atherosclerosis.[3] More recently, the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) report identified the metabolic syndrome as a risk factor for cardiovascular disease.[4] Evidence accumulated over the past decade shows that inflammation in the vasculature plays a role in the pathogenesis of the metabolic disease and subsequent vascular disease.[5,6] Components such as plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP), and fibrinogen are associated with an increased prevalence of these disease states. This review discusses the growing evidence regarding the mechanisms of inflammation and its relationship with the metabolic syndrome; biochemical markers of inflammation in the metabolic syndrome; and pharmacologic and nonpharmacologic methods that reduce inflammation and improve components of the metabolic syndrome.

**TAKE HOME POINTS**

- Insulin resistance, a key component of the metabolic syndrome, is linked to vascular inflammation and endothelial dysfunction, a hallmark of cardiovascular disease.
- Inflammatory markers such as C-reactive protein are predictors of cardiovascular events in healthy individuals as well as in persons with the metabolic syndrome.
- In patients with abdominal obesity, increased adipocyte expression of fatty acids and cytokines that induce insulin resistance may be an underlying mechanism linking inflammation and the metabolic syndrome.
- All patients with the metabolic syndrome should be encouraged to eat a diet low in saturated fats and to increase their level of physical activity, which improves insulin sensitivity and over the long term has an anti-inflammatory effect.
- Drugs that have been shown to have benefits in the metabolic syndrome include antidiabetic agents, lipid-lowering drugs, renin-angiotensin system antagonists, and antiplatelet agents.

## ADIPOSE TISSUE AND INFLAMMATION

Although the physiologic mechanisms linking inflammation and the metabolic syndrome have not been clearly defined, their association may be partly mediated by adipose tissue.[7] Adipocytes in adipose tissue are recognized as a source of potentially pathogenic molecules that may induce insulin resistance, including nonesterified fatty acids, cytokines, resistin, PAI-1, and leptin (**Figure 1**). When released into the systemic circulation, these molecules act as signals to tissues

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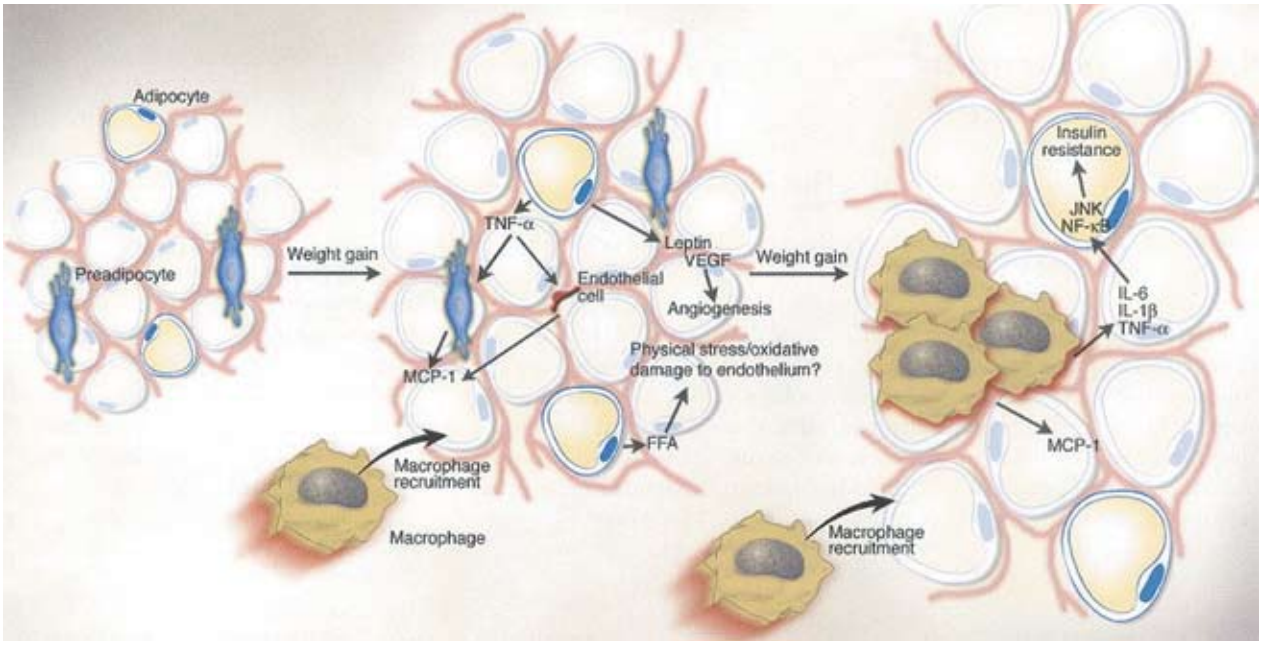


**Figure 1.** Adipocytes and inflammation. FFA = free fatty acid; IL = interleukin; JNK = jun N-terminal kinase; MCP = monocyte chemotactic protein; NF = nuclear factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor. (Adapted with permission from Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest 2003;112:1786.)

throughout the body. Systemic signaling by adipose tissue is suggested by the fact that obesity is accompanied by resistance to insulin in the liver (supplied mainly by portal blood) and in skeletal muscle (supplied through the systemic circulation). Moreover, the vascular dysfunction of obesity can be seen in conduit and resistance vessels, which also suggests a systemic signal from adipose tissue.[8] Thus, enhanced adipocyte expression of fatty acids and cytokines that induce insulin resistance may be a mechanism underlying the relationship between inflammation and the metabolic syndrome.

More recently, a group of adipose-generated cytokine-like molecules has been identified, collectively termed adipokines. These adipocyte-generated signals may have either local or systemic effects. Adipocytes secrete cytokines that are also secreted by inflammatory cell types such as macrophages. Macrophages and adipocytes have origins from different cell types and have different physiological functions, but both cell types are involved in lipid storage and cytokine production.[9] The cytokine tumor necrosis factor-α (TNF-α) influences insulin signaling through serine phosphorylation of the insulin receptor substrate-1, thereby inhibiting insulin action at the adipocyte level.[10] The cytokine interleukin (IL)-6 is an important systemic signal in infections and inflammatory states. IL-6 is the major cytokine that regulates hepatic production of CRP and insulin action in vascular disease. IL-6 and TNF-α have similar effects on insulin signaling and glucose transport, which might result in insulin resistance in several cell types.[6]

The adipose-derived protein adiponectin is also involved in adipose tissue signaling. Despite the adipocyte origins of this molecule, levels of adiponectin are inversely related to obesity. The control of adiponectin production remains to be investigated, but it is possible that adiponectin is subject to negative regulation by one or other adipokines acting in autocrine fashion.[11] It has been shown that adiponectin stimulates the production of nitric oxide in vascular endothelial cells, suggesting that adiponectin is protective to the vasculature.[12] The reduction of adiponectin levels in obesity suggests that these protective vascular effects are diminished in obese persons.

The adipokine leptin decreases insulin sensitivity and reduces insulin-stimulated glucose uptake in rat adipocytes.[13] The concentration of circulatory leptin is indirectly related to the amount of adipose tissue in the body, and elevation in the level of leptin is related to insulin resistance.[14] The functions of this hormone have not been established; however, the pathophysiologic mechanisms of various disease states appear to be directly correlated with leptin activity.[15] Skeletal muscle, adipose tissue, and liver are important insulin target tissues in the regulation of glucose metabolism.

**Table.** Actions of Insulin

| |
|---|
| Stimulatory |
| Promotes glucose transport into cells |
| Enhances glycogen synthesis |
| Increases fatty acid synthesis |
| Promotes protein synthesis |
| Modifies cellular differentiation and proliferation |
| Inhibitory |
| Inhibits gluconeogenesis |
| Reduces hepatic glucose output |
| Inhibits release of nonesterified fatty acids from adipose tissue |
| Suppresses lipid-related factors, including apolipoprotein B-100, apolipoprotein CIII, and hepatic lipase |

The presence of leptin receptor isoforms in these tissues indicates there is potential for direct peripheral effects of leptin on these tissues.[13,16] An understanding of the effects of leptin is needed to help clarify the apparent paradoxical role of this hormone in whole body glucose homeostasis.

## INSULIN RESISTANCE

Insulin is a hormone produced by the beta cells of the islets of Langerhans of the pancreas. Tissues throughout the body require insulin for the uptake and utilization of blood glucose. In patients with insulin resistance, the action of insulin at the cellular level is impaired, despite normal or even high levels of insulin in the blood (**Table**).

Although most types of tissue utilize glucose, skeletal muscle is the predominate site of glucose utilization. Insulin improves the uptake of glucose throughout most tissues. Elevated levels of glucose can lead to insulin resistance, thereby decreasing uptake of glucose by tissues and causing changes in the metabolic process. Skeletal muscle and the liver are major tissue sites of insulin resistance.[17,18] The initial action of insulin at the cellular level is to bind to the insulin receptor, and this binding activates signaling proteins within the cell to trigger metabolic processes. Insulin resistance can result because of changes or defects in insulin binding to the receptor or defects in the "post-receptor" setting.

Most patients with insulin resistance have the metabolic syndrome, but the connection between insulin resistance and the metabolic syndrome has not been fully defined.[19] Other factors such as genetics may be involved; that is, genetic factors in the presence of insulin resistance may trigger certain components of the metabolic syndrome such as dyslipidemia, elevated blood pressure, and hyperglycemia.[20,21]

The precise way in which insulin resistance develops is unclear, although genetics and lifestyle are believed to play a role.[22] By identifying patients with and at risk for insulin resistance, it may be possible to prevent some or all of the components of the syndrome. However, making a biochemical diagnosis of insulin resistance can be difficult.[23] Although fasting insulin levels correlate well with the degree of insulin resistance,[24] measurement of fasting insulin is not widespread. Standard methods for performing the test and definitions of normal and abnormal values have not been established.

Insulin resistance is central in the etiology of the metabolic syndrome, even though there is little clinical evidence that a reduction in insulin resistance will substantially improve any of the components of the metabolic syndrome other than glucose intolerance. Even though insulin resistance is associated with dyslipidemia and a proinflammatory state, it is less associated with hypertension. Additionally, there is little observed relationship between insulin resistance and the prothrombotic state observed in the metabolic syndrome.[2,25] Therefore, it is probable that many of the heterogeneous aspects observed in the metabolic syndrome are regulated independently of insulin resistance. Genetic factors and diet composition affect lipoprotein metabolism, and blood pressure regulation is affected by dietary factors, physical activity, and renal and adrenal function.

## ENDOTHELIAL DYSFUNCTION AND THE METABOLIC SYNDROME

Endothelial dysfunction is a hallmark of cardiovascular diseases such as coronary atherosclerosis. Endothelial dysfunction is most likely involved in both initiation and propagation of atherosclerosis (**Figure 2**).[26] Multiple investigations have demonstrated that patients with type 2 diabetes have impaired endothelial function, impaired nitric oxide–mediated vasodilation, and impaired vasodilation mediated independent of nitric oxide or prostacyclin.[27–29] Insulin resistance and the metabolic syndrome may be linked to endothelial dysfunction by several mechanisms. Insulin resistance is associated with endothelial dysfunction in that hyperinsulinemia causes the release of the potent vasoconstrictor endothelin. Also, the increased production of cytokines, low-grade inflammation (as reflected by elevated plasma levels of CRP), defects in insulin signaling pathways, activation of the renin-angiotensin system (RAS), and increased oxidative stress are associated with insulin resistance and could contribute to endothelial dysfunction.[30] Measurement of

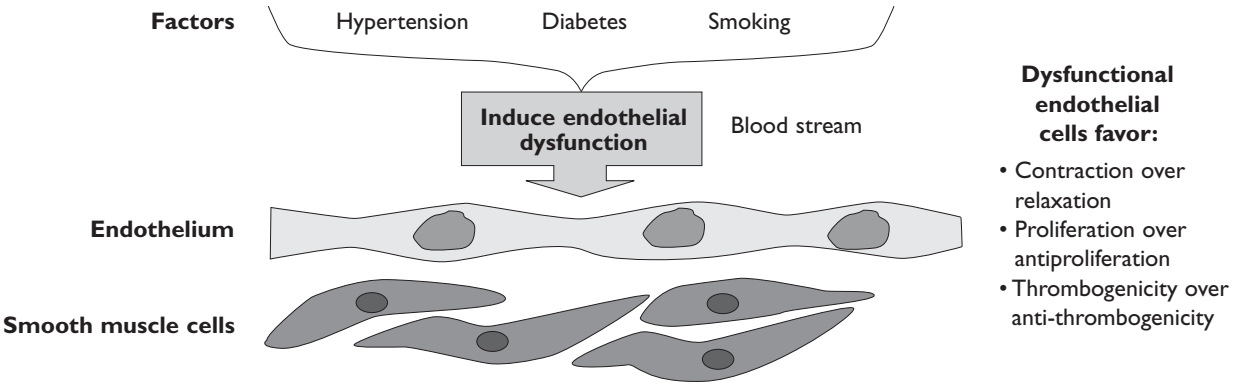


**Figure 2.** Endothelial dysfunction and vascular disease. (Adapted with permission from Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:843.)

these markers could be helpful in therapeutic management and control of the metabolic syndrome.

### Inflammatory Markers

Strong associations between inflammatory markers and the metabolic syndrome have been found in several epidemiologic studies.[31–34] Prospective studies have demonstrated associations between circulating levels of acute-phase proteins such as CRP and coronary events in healthy adult populations, patients with acute coronary syndromes, and patients with established macrovascular disease.[35,36] High-sensitivity CRP (hsCRP) assay is available in several clinical laboratories and can be utilized in an outpatient setting.

It has been proposed that chronic inflammation may function as a trigger for the metabolic syndrome.[37] Factors such as overnutrition, physical inactivity, and aging may cause cytokine hypersecretion and eventually lead to insulin resistance and diabetes in persons with genetic or metabolic profiles that predispose them to these conditions. Alternatively, resistance to the anti-inflammatory actions of insulin would result in increased blood levels of proinflammatory cytokines, causing a persistent low-grade inflammation. This proinflammatory state is associated with both insulin resistance and endothelial dysfunction. These observations suggest a connection between inflammation and metabolic processes that impair vascular functions.

The association between inflammation and atherosclerosis is well established. Chemokines seem to play a pivotal role in the pathogenesis of atherosclerosis, in part by attracting mononuclear cells to the vessel wall. Knockout-mice lacking monocyte chemotactic protein 1 (MCP-1) or IL-8 or their corresponding receptors have significantly reduced progression of atherosclerosis.[38] MCP-1 and IL-8 have been reported to trigger adhesion of monocytes to vascular endothelium under flow conditions.[39] MCP-1 is also involved in the activation of macrophages in the atheromatous plaque, and plasma levels are elevated in patients with acute myocardial infarction and unstable angina.[40,41]

Several studies have supported the hypothesis that insulin resistance may be associated with chronic subclinical inflammation. High glucose concentrations have been found to induce the release of IL-8 in endothelial and smooth muscle cells, possibly linking hyperglycemia, inflammation, and atherosclerosis.[42,43] CRP, IL-6, and TNF-α have been shown to be elevated in association with quantitative measures of insulin resistance.[44] Adipose tissue is metabolically active, and preadipocytes have been reported to secrete both MCP-1 and IL-8.[45]

Increased PAI-1 levels are associated with insulin resistance and atherothrombosis, and this association suggests a link between the metabolic syndrome and elevated risk for atherothrombotic disorders[46] (**Figure 3**). In addition, many coagulation and fibrinolytic proteins have been shown to be associated with features of the insulin resistance syndrome, and these associations suggest that some coagulation and fibrinolytic proteins have a role in atherothrombotic disorders.[47]

The hormone resistin was originally reported as an adipose tissue–specific hormone that provided a link between obesity and diabetes.[48] The level of resistin has been found to be elevated in obese mice and to be decreased by insulin-sensitizing thiazolidinediones (TZDs).[49] Resistin mRNA and protein levels decline in parallel with glucose and insulin during fasting and are restored after refeeding. Resistin expression in adipose tissue and serum levels of resistin are increased in response to hyperinsulinemia and further increased in response to hyperglycemia. These findings suggest that the nutritional regulation of resistin and changes in resistin gene expression and circulating levels in obesity

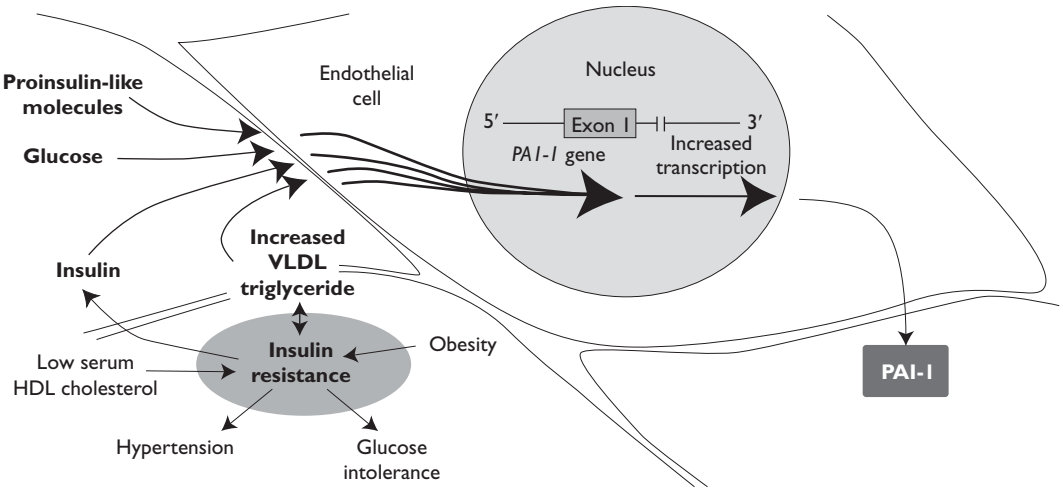


**Figure 3.** Plasminogen activator inhibitor-1 (PAI-1) and insulin resistance. PAI-1 levels are increased in the metabolic syndrome and decrease with weight loss. HDL = high-density lipoprotein;VLDL = very-low-density lipoprotein. (Adapted with permission from Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. N Engl J Med 2000;342:1796. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

are partly mediated by insulin and glucose.[48–50] In one study involving 879 asymptomatic patients, serum resistin levels were positively associated with levels of the inflammatory markers TNF-α, IL-6, and lipoprotein-associated phospholipase $A_2$. In patients with the metabolic syndrome, resistin levels more strongly predicted coronary artery calcification than CRP.[51]

Studies that measured urinary markers of inflammation have shown that microalbuminuria is a strong predictor of cardiovascular morbidity and mortality.[52,53] A recent study using multiple logistic regression analysis with microalbuminuria as a dependent factor clearly showed that all components of the metabolic syndrome except for obesity were associated with microalbuminuria.[54] Microalbuminuria has also been related to increased transcapillary albumin leakage and may represent a surrogate measure of endothelial dysfunction.[55] Whether insulin resistance is involved in the pathogenesis of microalbuminuria may be less important than the fact that microalbuminuria indicates an advanced stage of cardiovascular disease and is a predictor of high cardiovascular mortality.

## METHODS TO REGULATE THE MECHANISMS OF INFLAMMATION

Currently, no randomized controlled trials specifically examining the treatment of metabolic syndrome have been published.[56] The reason for this difficulty is that determining clinical endpoints in patients with the metabolic syndrome requires a long time frame and a large number of subjects to obtain statistical significance and power. The proposed length and number of subjects for such a trial would result in a significant dropout rate and reduced rate of compliance with therapy. Therefore, it is necessary to study endpoints (eg, changes in blood pressure, weight loss, lipid profile) that can be measured in an office-based setting, or to observe changes in inflammatory markers or endothelial function using accepted techniques. 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.

### Lifestyle Changes: Diet and Exercise

All patients diagnosed with the metabolic syndrome should be encouraged to change their diet and exercise habits as primary therapy. Weight loss improves all aspects of the metabolic syndrome and reduces cardiovascular mortality and all-cause mortality.[57] The amount and quality of fat in the diet could be important for the development of insulin resistance and related inflammatory activity. A high proportion of long-chain unsaturated fatty acids and a low proportion of saturated fatty acids in the diet have been associated with improved insulin action.[58] Highly unsaturated fatty acids, and n-3 fatty acids in particular, are receiving increasing attention as potential anti-inflammatory agents. It is well known that dietary fatty acids appear to modulate the release of different cytokines. A recent randomized trial demonstrated that production of IL-6 and other cytokines by peripheral mononuclear cells was significantly decreased after dietary polyunsaturated fatty acid supplementation.[59] Serum fatty acid concentration

reflects to some extent the composition of dietary fat. It has been observed that the percentage of saturated fatty acids and n-6 fatty acids was significantly associated with circulating IL-6, whereas the percentage of n-3 fatty acids correlated negatively with CRP levels in overweight individuals. Saturated-to-n-3 and saturated-to-n-6 fatty acid ratios were significantly and positively associated with CRP and IL-6, respectively. These associations suggest that obesity is an inflammatory disease of dietary origin.[60,61]

As the most insulin-sensitive tissue in the body, skeletal muscle is a primary target for impacting insulin resistance. Aerobic exercise reduces glucose and lipid levels in skeletal muscle and is effective in improving sensitivity of the insulin receptor. The effects of exercise on insulin sensitivity are rapid in onset and can last 3 to 5 days.[57] Exercise produces a short-term, inflammatory response, whereas both cross-sectional comparisons and longitudinal exercise training studies demonstrate a long-term anti-inflammatory effect. This anti-inflammatory response may contribute to the beneficial effects of habitual physical activity.[62]

### Hypoglycemic Drugs

**Metformin.** Metformin is widely used in the treatment of diabetes. Metformin has been shown to decrease insulin resistance and reduce hyperglycemia through effects on hepatic glucose production in vivo in hyperglycemic patients with type 2 diabetes.[63–65] Additionally, it has been observed that metformin does not alter overall insulin sensitivity in the body and its effects are specific to certain tissues.[66,67] Several studies also report that metformin therapy improves peripheral insulin sensitivity.[68–72]

**Thiazolidinediones.** Insulin secretion is increased in the setting of the metabolic syndrome, and subsequent progressive dysfunction of the beta cell occurs as a result of the adverse effects of hyperglycemia, insulin resistance, and excess fatty acids.[73] TZDs decrease insulin resistance and prevent the decline in beta-cell mass. Previous data have suggested that treatment with troglitazone in obese patients with impaired glucose tolerance reduces fasting insulin levels and improves glucose tolerance.[74] In the Troglitazone in Prevention of Diabetes (TRIPOD) study,[75] high-risk patients randomized to troglitazone had a 56% reduction in the incidence of diabetes. Furthermore, the results suggested sustained prevention after withdrawal of troglitazone. There may be benefits of TZD treatment extending beyond diabetes prevention to the prevention of cardiovascular complications of the metabolic syndrome. These agents have many effects on several aspects of the metabolic syndrome: lowering blood pressure, improving dyslipidemia, reducing inflammatory markers, and decreasing the procoagulative state.[76] In the TRIPOD study,[75] there was a reduction in carotid intima-media thickness in the group of patients treated with troglitazone. The multiple beneficial effects of TZDs appear to be significant and are not seen to the same extent with other hypoglycemic agents.

### Renin-Angiotensin System Antagonists

The RAS plays a central role in the pathogenesis of atherosclerosis-related diseases and may have a significant impact on the progression of the metabolic syndrome. Angiotensin II, the central molecule in the RAS, has multiple effects on inflammation, oxidation, and atherosclerotic plaque initiation and progression.[77] In a short-term study, therapy with the angiotensin-converting-enzyme inhibitor quinapril in patients with the metabolic syndrome increased erythrocyte superoxide dismutase activity and decreased levels of the proinflammatory and pro-oxidative marker 8-isoprostane. Also, quinapril administration inhibited the conversion of low-density lipoprotein (LDL) cholesterol to the more atherogenic oxidized LDL.[78] In another study, the angiotensin II blocker irbesartan in conjunction with lipoic acid improved endothelial function and reduced the levels of soluble IL-6 and PAI-1 in patients with the metabolic syndrome.[79] These findings suggest that RAS inhibitors have powerful vascular anti-inflammatory and anti-oxidative effects.

### Lipid-Lowering Agents

**Statins.** The beneficial effects of statins (hydroxymethylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) on cardiovascular disease have been generally attributed to cholesterol lowering. There is growing in vitro and in vivo evidence that statins have an anti-inflammatory effect that may be independent of lipid lowering. Statins have been shown to lower CRP levels in post–myocardial infarction patients (independently of cholesterol levels) and in patients with type 2 diabetes.[80,81] Statins can act through both HMG-CoA reductase-dependent mechanisms and HMG-CoA reductase-independent means.[82] In coronary atherosclerosis, peripheral arterial disease, and diabetes, the beneficial effect of the drugs might be attributed to their LDL-lowering activities, their anti-inflammatory activities, or both. If statins inhibit the acute phase response by diminishing the intravascular deposition of cholesterol and phospholipids, more potent statin treatment will probably not interfere with acute phase responses to infection, injury, and other types of stress. The prospective JUPITER study[83] seeks

to determine whether a powerful statin, such as rosuvastatin, prevents cardiovascular disease among patients who have normal LDL cholesterol levels but have an increased level of hsCRP. Many of these subjects will have several components of the metabolic syndrome.[83]

**Fibrates.** Fibrates appear to be especially effective in patients whose primary lipid disorder is a disturbance of the triglyceride–high-density lipoprotein axis. Fibrates also favorably modify atherogenic dyslipidemia and may directly reduce atherogenesis. Post hoc analysis of recent fibrate trials implies that there is a reduction in cardiovascular endpoints in patients with the metabolic syndrome.[84] Fibrates also appear to influence hemostatic and inflammatory markers and indicators of improved vascular wall biology. These findings suggest a beneficial effect in the metabolic syndrome.[85]

### Antiplatelet Agents

No prospective clinical studies regarding the role of aspirin in preventing or reducing clinical outcomes in patients with the metabolic syndrome have been conducted. No drugs are available that target prothrombotic markers such as PAI-1 and fibrinogen. An alternative approach to ameliorating the prothrombotic state is antiplatelet therapy. Use of aspirin for primary prevention in patients with metabolic syndrome is promising.[2] According to current recommendations, low-dose aspirin therapy has a favorable efficacy/side effect ratio when 10-year risk for CHD is 10%. There is substantial evidence that demonstrates the anti-inflammatory effects of aspirin. As an inhibitor of the cyclooxygenase enzyme, aspirin inhibits the activity of inflammatory prostaglandins and the prothrombotic molecule thromboxane. Because of its beneficial effects in primary prevention (high-risk individuals) and secondary prevention of atherosclerosis, relatively low side-effect profile, and low cost, aspirin may have significant effects as an anti-inflammatory agent in the treatment of the metabolic syndrome.

There is no clear evidence that clopidogrel or ticlopidine have benefits in the metabolic syndrome. Clopidogrel is a thienopyridine agent that antagonizes the adenosine diphosphate (ADP) receptor. In addition to its effect as an antiplatelet agent, clopidogrel may have an effect on the response to inflammation.[86] Clopidogrel decreases expression of P-selectin, which plays a key role in platelet-neutrophil communication.[87] Clopidogrel has also been shown to reduce the ADP-induced expression of CD40 ligand, an important mediator of platelet interaction with inflammatory cells.[88,89] This ability to interrupt the platelet–endothelial–monocyte cascade may give clopidogrel an anti-inflammatory benefit beyond its antiplatelet activity. Thus, the antiplatelet and anti-inflammation mechanisms of agents such as aspirin and clopidogrel appear to function together, suggesting a role for these agents in management of the metabolic syndrome.[90,91]

## SUMMARY

The metabolic syndrome is a significant risk factor for cardiovascular disease, and insulin resistance plays a major role in the initiation of this disease. Although the physiologic mechanisms linking inflammation and the metabolic syndrome have not been clearly defined, their association may be mediated by adipose tissue. Adipose tissue is a source of several molecules that are potentially pathogenic in cardiovascular disease, including cytokines and adipokines.

The metabolic syndrome may be associated with chronic subclinical inflammation and increased activity of markers of inflammation in various types of tissue. Inflammatory markers are predictors of cardiovascular events and progression to diabetes in healthy individuals as well as those with the metabolic syndrome. Two inflammatory markers that generally can be measured in commercial laboratories include high-sensitivity C-reactive protein and microalbuminuria.

Based on clinical trials, aggressive management of the individual components of the metabolic syndrome should make it possible to prevent or delay the onset of diabetes, hypertension, and/or cardiovascular disease. Lifestyle changes, including diet and exercise intervention, have been shown to improve endothelial function and reduce inflammatory activity in the vasculature. Several classes of cardiovascular drugs have been shown to have mechanistic benefits in the metabolic syndrome; these include antidiabetic drugs, lipid-lowering drugs, renin-angiotensin system antagonists, and antiplatelet agents. **HP**

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