The vascular endothelium and CAD:
New target considerations in treating the cardiovascular dysmetabolic syndrome

A CME program based on the lectures and discussions from the National Faculty Meeting of the Vascular Biology Working Group

√ Hypertension
√ Dyslipidemia
√ Insulin resistance
√ Special populations

Published under the auspices of the Vascular Biology Working Group
Educational Goals

Upon successful completion of this continuing education program, you should be able to:

- Discuss the cardiovascular dysmetabolic syndrome and how it leads to adverse clinical events
- Describe the component risks of the cardiovascular dysmetabolic syndrome and how they negatively impact the vessel wall and endothelial function
- Employ therapeutic options for improving endothelial function and decreasing cardiovascular morbidity and mortality

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“IVUS studies show that by the time the first angiographic lesion is evident, at least 80% of other sites in the coronary circulation meet rigorous criteria for atherosclerosis.”
— Steven E. Nissen, MD
A clustering of metabolic abnormalities, including insulin resistance, dyslipidemia, hypertension, and obesity, is recognized as being associated with a substantially increased risk of cardiovascular disease. Formerly called syndrome X or the insulin-resistance syndrome, this grouping of metabolic anomalies is now known also as the cardiovascular dysmetabolic syndrome (CDS). When these metabolic disorders occur together, they greatly increase the risk of cardiovascular morbidity and mortality (Figure 1). People with CDS are either insulin resistant or have frank diabetes. The prevalence of coronary artery disease in persons with type 2 diabetes is at least 4 times greater than among nondiabetic individuals. Among hospitalized patients aged 55 or less with myocardial infarction, a large majority have type 2 diabetes or are insulin resistant. Well over 50% of these patients have CDS.

Insulin resistance disrupts fibrinolysis

Syndromes of insulin resistance and hyperinsulinemia, including type 2 diabetes and polycystic ovary syndrome, are associated with a derangement in vessel wall fibrinolytic system proteins that can cause inhibition of proteolysis. Studies reveal very high concentrations of tissue plasminogen activator inhibitor type 1 (PAI-1) in the blood of diabetic and obese insulin-resistant subjects that inhibit fibrinolytic system activity in blood. Atheroma extracted from vessels of patients with type 2 diabetes also have marked elevations in PAI-1 relative to concentrations of urokinase (u-PA) (Figure 2).

These observations support the hypothesis that one factor in the development of accelerated macroangiopathy in type 2 diabetes is altered expression of fibrinolytic system components in atheroma, and presumably in vessel walls. Inhibition of fibrinolytic system activity in insulin-
resistant states leads to persistence of thrombosis, paving the way for thrombotic coronary artery occlusion and accelerated atherosclerosis or restenosis in response to clot-associated mitogens. Studies show that people with type 2 diabetes who undergo angioplasty are 4 times more likely to die within 5 years than nondiabetic individuals with similar lesions who receive similar treatment. Their poor long-term prognosis is largely the result of accelerated restenosis.

**Increased PAI-1 affects plaque formation**

Elevated PAI-1 levels may foster the development of unstable plaque in persons with type 2 diabetes or other insulin-resistant states consistent with the following hypothesis. High PAI-1 concentrations inhibit the formation of plasmin. Reduction of this proteolytic enzyme decreases the degradation of extracellular matrix, preventing vascular smooth muscle cell (VSMC) migration into the neointima. The resulting plaque has a high lipid-to-VSMC ratio and a thin fibrous cap that is vulnerable to rupture. The plaque contains relatively few VSMCs, numerous macrophages and lipid-laden macrophage-derived foam cells. The composition and vulnerability of plaque have been identified as chief determinants for the development of acute coronary syndromes.

**Troglitazone lowers PAI-1: The fibrinolytic system as a therapeutic target**

Vascular wall PAI-1 synthesis may be a potentially important target for efforts that are intended to slow accelerated macroangiopathy in type 2 diabetes and other insulin-resistant states. Administration of troglitazone, a thiazolidinedione that enhances insulin sensitivity, to women with polycystic ovary syndrome improved insulin sensitivity and significantly reduced PAI-1 levels (Figure 3). It appears that increasing insulin sensitivity may help lower the imbalance in PAI-1 expression in the vessel wall and could influence its potentially atherogenic effects.

Figure 3: PAI-1 antigen and activity levels before and after treatment with troglitazine. A concordant decline in both PAI-1 antigen and activity levels was observed in response to treatment. Data are the mean ± SEM. Adapted from Ehrmann DA et al.

"Directing therapy to the vessel wall fibrinolytic system offers a promising approach to slow macrovascular disease progression and diminishes the threat of acute coronary events in patients with type 2 diabetes and other insulin-resistant states."
New research into the pathogenesis of hypertension and atherosclerosis has traced their origins to the endothelium. Increasingly recognized as the "maestro" of the cardiovascular system, the endothelium contributes to the regulation of vascular tone and structure, sending and responding to a multitude of stimuli and triggering vasoactive systems that influence vascular homeostasis. Normal endothelial function exists only when there is a balance between vasoactive substances, such as the vasodilator nitric oxide (NO), and vasoconstrictors, such as angiotensin II (A II). Hypertension is the most common risk factor for endothelial dysfunction. Disruptions in endothelial function that affect the regulation of tone, hemostasis, and vessel structure accelerate hypertension and lead to atherosclerosis and heart failure.

Hypertension: A disease of the vasculature

In chronic hypertension, NO activity is reduced and A II activity is increased under the influence of angiotensin-converting enzyme (ACE). Elevated A II levels have unique vascular effects; they increase vascular smooth muscle superoxide ion production, which inhibits endothelium-dependent vasodilation, probably by degradation of endothelium-derived NO. The two hallmarks of endothelial dysfunction, impaired vasorelaxation and enhanced release of inflammatory mediators, appear to be outcomes of reductions in NO. In addition to being a potent vasodilator, NO inhibits cell growth and exerts antithrombotic, anti-inflammatory, antioxidant, and antiatherogenic effects. Angiotensin II affects the cardiovascular system through vasoconstriction, induction of cell growth, modulation of myocardial hypertrophy, fibrosis, and ventricular remodeling.

A central role for oxidative stress

One of the earliest changes associated with hypertension is an increase in oxidative stress. This effect may be the common cause of endothelial dysfunction that contributes to the development and progression of atherosclerosis and ischemic disease in association with hypertension and a variety of other cardiovascular risk factors. The changes caused by oxidative stress, including a decrease in NO and an increase in tissue ACE and local mediators, lead to thrombosis, inflammation, vasoconstriction, vascular remodeling, and plaque rupture. A II plays a major role in generation of superoxide by increasing the activity of membrane-bound oxidases (NADH/NADPH).

The role of the RAS and tissue ACE

The renin-angiotensin system (RAS) is a fundamental mediator of vascular endothelial function. The RAS may be viewed as functioning in 2 different environments. The circulating RAS is responsible for acute blood pressure and intravascular volume regulation, while the tissue RAS is implicated in long-term changes that affect vascular and cardiac structure and function. Less than 10% of ACE circulates in the plasma, while over 90% is found in tissues (eg, blood vessels, heart, CNS). Elevated levels of tissue ACE have been associated with a substantial increase in vascular dysfunction and atherosclerotic changes, likely reflecting the adverse influence of increased levels of A II and other vasoactive substances (PAI-I, thromboxane A₂, etc).

ACE inhibition protects the vessel wall

In addition to their systemic blood-pressure lowering effect, ACE inhibitors have many favorable effects on the endothelium (Figure). They produce a decrease in A II levels and an accumulation of bradykinin that promotes the release of NO, resulting in vasodilation and relaxation of vascular smooth muscle. ACE inhibition blunts the production of superoxide anions that is associated with increased A II. It reduces vascular smooth muscle cell growth and migration, decreases platelet aggregation, and helps maintain fibrinolytic balance by decreasing PAI-1 and increasing t-PA levels.
Figure: Vasculoprotective effects of ACE inhibitors. Adapted from Dzau VJ et al. 4

JNC VI guidelines for initial treatment with ACE inhibitors

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) recommends ACE inhibitors as initial treatment for a broad segment of hypertensive patients including those with comorbid heart failure, myocardial infarction with systolic dysfunction, and type I and type II diabetes with proteinuria (Table). ACE inhibitors are also recommended for patients with renal insufficiency due to other causes in the absence of significant bilateral renal artery stenosis.

Studies show that ACE inhibitors exhibit a wide range of ACE-binding affinity in tissue and plasma. Quinaprilat, the active metabolite of quinapril, demonstrates the greatest degree of ACE-binding affinity in both tissue and plasma. Given the key role of tissue ACE and the endothelium in hypertension and atherosclerosis it seems plausible that the differences among ACE inhibitors in tissue binding could translate into differences in clinical response.

Uncomplicated hypertension
- Diuretics
- β-Blockers

Compelling Indications
Heart failure
- ACE inhibitors
- Diuretics

Diabetes mellitus (Type I) with proteinuria
- ACE inhibitors

Myocardial infarction
- β-Blockers (Non-HSA)
- ACE inhibitors (with systolic dysfunction)

Isolated systolic hypertension (older persons)
- Diuretics preferred
- Long-acting dihydropyridine calcium channel antagonists

Table: JNC VI indications for ACE inhibitors as initial antihypertensive therapy. Adapted from The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. 2

“In addition to their systemic blood-pressure lowering effect, ACE inhibitors have many favorable effects on the endothelium.”
Review of recent clinical trials to improve endothelial function

Carl J. Pepine, M.D., Professor and Chief of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, Fla

In a series of recent clinical trials, ACE inhibitors, and especially those agents with high tissue affinity, have demonstrated a significant ability to improve endothelial function and enhance cardiovascular health. These trials support the concept that high tissue ACE affinity is likely advantageous for improving endothelial function in coronary artery disease.

Enalaprilat vs quinaprilat in heart failure patients

A study by Hornig and coworkers compared the effects of quinaprilat and enalaprilat on endothelium-mediated flow-dependent dilation (FDD) in patients with chronic heart failure. Quinaprilat improved FDD by more than 40%, whereas enalaprilat had no effect (Figure 1). Increasing the dose of enalaprilat to the level where hypotension occurred did not improve FDD (Figure 2). Quinaprilat increased NO-mediated flow by more than 100%, suggesting that the improvement in endothelial function was the result of increased NO availability.

Since the ACE inhibitor doses used were similarly able to block the conversion of angiotensin I to angiotensin II, the difference in endothelium-mediated FDD was attributed to an intrinsic difference in tissue affinity between the 2 agents. Quinapril is high in tissue-ACE binding capability, while enalapril is low. Tissue-ACE affinity may be essential for improving endothelium-mediated FDD with short-term ACE inhibition.

TREND (Trial on Reversing ENdothelial Dysfunction)

The TREND study was conducted in 129 normotensive patients with coronary artery disease (CAD) and preserved left ventricular function to determine the effects of quinapril on endothelium-mediated dilation. This randomized, double-blind, placebo-controlled study included patients with single- or multi-vessel disease (>50% stenosis) and endothelial dysfunction. After 6 months of treatment, quinapril (40 mg) significantly prevented constriction in coronary artery segments independently of blood pressure changes. A 5% improvement in coronary artery segment diameter was significantly more frequent in the quinapril-assigned patients, while 5% deterioration was more frequent with placebo (Figure 3).
Figure 3: Endothelial function and ACE inhibition: TRENDS results. Adapted from Mancini et al.²

BANFF (Brachial Artery ultrasound Normalization of Forearm Flow)

The BANFF trial compared the effects of 4 vasodilator agents on endothelial function in patients with CAD by measuring changes in FDD.³ The agents given were the ACE inhibitors quinapril (20 mg, n = 56) and enalapril (10 mg, n = 55), the angiotensin II inhibitor losartan (50 mg, n = 38), and the calcium antagonist amlodipine (5 mg, n = 45). After 8 weeks of treatment, only quinapril was associated with a significant improvement in FDD (Figure 2). The results suggest that ACE inhibitors, as well as other antihypertensive agents, are likely to differ in their ability to improve endothelial function.

Figure 4: BANFF: Absolute changes in flow-dependent dilation. Adapted from Anderson TJ et al.³

QUO VADIS (effects of QUinapril On Vascular ACE and Determinants of ISchemia)

The QUO VADIS study was a randomized, double-blind, placebo-controlled trial studying the effect of quinapril (40 mg/day) on ischemia in 187 patients who underwent coronary artery bypass grafting (CABG). In part 1 of the study, preoperative treatment with quinapril but not captopril blocked the conversion of angiotensin I to angiotensin II in segments of the internal artery removed at surgery. This and improved vascular response suggest functional differences between the drugs.⁴

In part 2 of the study, patients were followed for 1 year to determine the effect of quinapril on the reduction of ischemic events after CABG.⁵ Quinapril treatment resulted in a significant and clinically relevant risk reduction in ischemic events, 4% vs 18% with placebo (Figure 5). Improvements in exercise duration and ischemic ST-segment changes during ambulatory ECG monitoring were comparable in both groups.

Figure 5: QUO VADIS: Effects of quinapril on ischemia. Adapted from Oosterga M et al.⁵
HOPE (Heart Outcomes Prevention Evaluation)

The HOPE study was a randomized, placebo-controlled trial conducted in 267 centers in 19 countries in North and South America and Europe over 4 1/2 years. The subjects included 9,541 patients > 55 years old who were at high risk for cardiovascular events due to a history of ischemic heart disease, peripheral artery disease, stroke, or diabetes plus 1 risk factor. Patients with reduced ejection fractions or clinical heart failure were excluded (Figure 6). The 2x2 factorial design examined the impact of tissue ACE inhibition with ramipril (10 mg daily) or placebo on cardiovascular outcomes and vitamin E (400 mg daily) or placebo on cardiovascular outcomes and cancer.

The ACE inhibitor arm was stopped early due to a consistent and highly significant benefit of tissue ACE inhibition. There was a 22% decline in the combined incidence of cardiovascular death, nonfatal myocardial infarction (MI), and stroke. The risk of cardiovascular death declined by 24%, nonfatal MI by 22%, nonfatal stroke by 32%, new or worsening heart failure by 15%, emergency revascularization by 15%, and hospitalizations for heart failure by 16% (Figure 7). Patients benefited from ACE inhibition regardless of age, gender, or the presence or absence of hypertension or diabetes. The findings from HOPE support and extend those of TRENDD, BANFF, and QUO VADIS in confirming the benefits of tissue ACE inhibition, which until now were only demonstrated in heart failure or acute MI.

As an aggregate, these trials demonstrate that the endothelium is a critically important regulator of blood flow that can be targeted effectively with ACE inhibition therapy. These findings also suggest that ACE inhibition with agents that have a high tissue affinity (quinapril, ramipril, and trandolapril) may be of particular benefit in enhancing vascular function and potentially improving cardiovascular outcomes.
A lot of our beliefs about how we manage lipids are derived from 5 major statin trials:

**Primary Prevention Trials**
- WOSCOPS (West of Scotland Coronary Prevention Study)\(^1\)
- AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study)\(^2\)

**Secondary Prevention Trials**
- 4S (Scandinavian Simvastatin Survival Study Group)\(^3\)
- CARE (Cholesterol and Recurrent Events Trial)\(^4\)
- LIPID (Long-term Intervention with Pravastatin in Ischemic Disease)\(^5\)

The findings are:
- Consistent reductions in LDL-C between 25% and 35%, without significant adverse effects
- Clinical benefits observed at various baseline LDL-C levels, including levels near “normal” found in the U.S. population
- Reductions in cardiovascular and overall mortality generally appear within 2 years
- Studies support treatment in various patient populations, including men, women, diabetics and the elderly.

Statins improve endothelial function...

In addition to the 5 major statin trials, our emerging knowledge of the endothelium is influencing our approaches to therapy. Treating dyslipidemia with statin drugs appears to improve endothelial function.\(^6,7\) Statin agents also exert a rapid, highly efficacious improvement in vasoactivity through their effect on the NO system.\(^8\) It is also apparent that statin agents can exert short-term improvement in endothelial function. In the study by O’Driscoll et al.,\(^9\) within a month of statin therapy, there is a significant increase in blood flow.

Figure 1: Effects of cholesterol lowering on myocardial ischemia. Adapted from Andrews TC et al.\(^10\)

... and ischemic events

Beneficial effects on the endothelium likely correlate with changes in ischemic events. Groups working at the Brigham and Women’s Hospital and Harvard Medical School used the measurements of ST-segment depression on ambulatory ECG in patients with CAD. They enrolled 40 patients with proven CAD, total serum cholesterol between 191 and 327 mg/dL, and at least 1 episode of ST-segment depression on ambulatory ECG monitoring. Patients were randomized to either an AHA Step 2 diet plus placebo, or to the same diet plus treatment with lovastatin. Figure 1 shows the patient-by-patient effect of cholesterol lowering over 6 months on the number of episodes of ischemic ST-segment depression. Two of 20 in the placebo group vs 13 of 20 in the treatment group show resolution of ischemia.\(^10\)

The mandate for aggressive LDL-C reduction

There appears from all the trial data no doubt that the lower you put the LDL-C, the lower the risk of developing a coronary event. The trial that was specifically designed
to look at the concept of whether lower is better is the Post-Coronary Artery Bypass Graft (CABG) trial. This study sample included 1351 participants who were one to 11 years post-CABG surgery. Each of the men in the study had at least two patent saphenous vein graphs, and each of the women participants had at least one. The LDL-C levels were 130 to 175 mg/dL after being on a diet.

Patients were randomized and blinded to the intensity of treatment, which consisted of lovastatin at 40 to 80 mg/day plus or minus cholestyramine 8 mg/day or lovastatin 2.5 to 5 mg/day plus or minus cholestyramine 8 mg/day. The goal was to reach an aggressive target LDL-C of less than 85 mg/dL, and a moderate target LDL-C of 130 to 140 mg/dL. Study outcomes were a mean per-patient percent of grafts with significant progression in SVG greater than a 0.6 mm change. The secondary endpoint was the occurrence of new occlusions and lesions plus lumen narrowing.

Figure 2: Post-CABG: Aggressive vs moderate LDL-C reduction. *Mean achieved. Adapted from Post-CABG Investigators.

<table>
<thead>
<tr>
<th></th>
<th>Moderate</th>
<th>Aggressive</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>39</td>
<td>26</td>
<td>-28</td>
</tr>
<tr>
<td>New occlusions</td>
<td>15</td>
<td>10</td>
<td>-40</td>
</tr>
<tr>
<td>New lesions</td>
<td>21</td>
<td>10</td>
<td>-52</td>
</tr>
<tr>
<td>Mean lumen change (mm)</td>
<td>-0.38</td>
<td>-0.20</td>
<td>-48</td>
</tr>
</tbody>
</table>

Figure 3: Post-CABG: Effect of aggressive vs moderate LDL-C reduction on CAD progression. *MRE = Mean per-patient percentage of grafts. Adapted from Post-CABG Investigators.

In all study parameters, there was consistently greater benefit in the group of patients whose LDL-C was treated aggressively (Figure 3). The primary conclusion of the post-CABG trial is that by achieving a mean LDL-C of 95 mg/dL, there is greater benefit than if the patient carries a mean LDL-C of 135 mg/dL.

**AVERT Trial: Aggressive LDL-C lowering reduces ischemic events**

The second trial that suggests the urgent need for aggressive lowering of LDL-C is the Atorvastatin Versus Revascularization Treatments (AVERT) study. This trial was designed to evaluate the effects of aggressive lipid lowering with atorvastatin on cardiovascular ischemic events in a stable CAD patient population, who were scheduled to undergo a revascularization procedure followed by usual care. A total of 341 patients were randomized at 37 centers in the United States, Canada, and Europe between July 1995 and December 1996.
AVERT was an 18-month open-label, randomized, multicenter study of patients with a recommendation for percutaneous revascularization, with ≥1 native coronary segment with ≥50% stenosis, LDL-C ≥115 mg/dL (≥3.0 mmol/L), TG ≤500 mg/dL (≤5.6 mmol/L), LVEF ≥40%, and the ability to complete 4 min of a Bruce treadmill protocol or a 20 W/min bicycle exercise test without ≥2 mm ST segment depression. Patients were randomized to either medical therapy with atorvastatin 80 mg/day plus usual medical therapy, or angioplasty plus usual care, which could include lipid-lowering therapy.

**AVERT conclusions**

Results of the AVERT study showed that 22 patients in the atorvastatin group (13%) and 37 in the angioplasty group (21%) experienced ischemic events (a difference of 36%) (Figure 4). Time to an ischemic event was significantly longer in the atorvastatin group (Figure 5). The results showed that aggressive lipid-lowering with atorvastatin resulted in a mean serum LDL-C level of 77 mg/dL. As with the Post-CABG trial, this data supports the NCEP recommendations of a target LDL-C of less than 100 mg/dL in patients with coronary heart disease.

<table>
<thead>
<tr>
<th>Ischemic Event</th>
<th>Atorvastatin Group (N=164)</th>
<th>Angioplasty Group (N=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Any ischemic event</td>
<td>22</td>
<td>37</td>
</tr>
</tbody>
</table>

"The primary conclusion of the post-CABG trial is that by achieving a mean LDL-C of 95 mg/dL, there is greater benefit than if the patient carries a mean LDL-C of 135 mg/dL."
One of the most promising new areas of investigation into atherosclerosis at the molecular level stems from research on transcriptional regulation of proteins that are critically involved in atherogenesis. Over the past year, the peroxisomal proliferator-activated receptors (PPARs), members of the nuclear receptor superfamily (e.g., estrogen receptor) have been identified as potential links between cardiovascular dysmetabolic syndrome, insulin resistance, and atherosclerosis. PPARs (α, β, γ), as ligand-activated transcription factors, regulate the expression of target genes.

**PPARγ acts in lipid metabolism and adipogenesis...**

PPARγ, known to be expressed primarily in fat and liver cells, plays a critical role in regulating genes involved in adipogenesis, glucose homeostasis, and lipid metabolism (Figure). Ligands for PPARγ include prostaglandin metabolites and synthetic thiazolidinediones, a new class of antidiabetic compounds. Troglitazone is the first in this class of agents, which are thought to improve insulin resistance through a nuclear mechanism of action independent of the insulin receptor.

![Figure: PPARγ plays a “critical role in adipogenesis, glucose metabolism, lipid metabolism, and possibly vascular signaling.” Adapted from Plutzky J.](image)

... and as a mediator of vascular disease

This past year, numerous studies demonstrated a role for PPARs in vascular biology and possibly atherosclerosis. Several of these studies implicated PPARγ in the expression of matrix metalloproteinases (MMPs), particularly MMP-9. These enzymes participate in extracellular matrix degradation, thus possibly influencing VSMC migration, atherogenesis, plaque rupture, and restenosis after arterial interventions. PPARγ is expressed in atherosclerotic lesions where it may regulate MMP-9 expression. Activation of PPARγ with troglitazone or a natural ligand decreases MMP-9 activity in a dose-dependent manner. In vitro studies show that PPARγ activators inhibit the expression of inducible NO synthase, scavenger receptor A, and MMP-9 in monocyte cell lines.

In VSMCs, either troglitazone or a natural ligand inhibit both MMP-9 activity and growth factor-induced VSMC migration. This could have an impact on arterial remodeling in hypertension and atherosclerosis, as also implied by studies suggesting troglitazone effects on VSMC proliferation. PPARα activators lacked such effect, indicating that PPAR activity is specific. PPARα is expressed in endothelial cells, where it regulates vascular adhesion molecule expression, suggesting its potential importance in atherosclerosis.

**Looking ahead**

The availability of therapies like troglitazone that operate at the molecular level by activating gene transcription factors may allow fundamental interventions in disease processes.

“The involvement of PPARs in lipid metabolism, adipogenesis, glycemic responses, and vascular biology suggests that they may be a key to understanding factors that promote atherosclerosis and its clinical sequelae.”
Glucose control and insulin resistance: New mechanistic insights

Peter N. Weissman, M.D., Clinical Assistant Professor of Internal Medicine/Endocrinology, University of Miami, Florida, Adjunct Director, Continuing Medical Education, Joslin Diabetes Center, Boston, Mass

Current therapy for diabetes is based on an understanding of the mechanisms of hyperglycemia and the role of insulin resistance. Hyperglycemia results from peripheral insulin resistance leading to decreased insulin-mediated glucose disposal and to increased overnight hepatic glucose production, and from insufficient pancreatic insulin secretion. Both hyperinsulinemia and hyperglycemia increase the risk of macrovascular disease, making strict glycemic control and reduction of insulin resistance essential to the control of diabetes and the improvement of cardiovascular outcomes.

Pharmacology and pathophysiology

The oral agents for glucose control — sulfonylureas, α-glucosidase inhibitors, biguanides, and thiazolidinediones — target different pathophysiologic mechanisms of diabetes. Sulfonylureas increase endogenous insulin by enhancing glucose-mediated secretion by pancreatic β cells; the α-glucosidase inhibitors (acarbose and miglitol) decrease postprandial hyperglycemia by delaying carbohydrate absorption. While any treatment that decreases hyperglycemia results in an increase in insulin sensitivity, neither sulfonylureas nor α-glucosidase inhibitors directly lower insulin resistance.

The biguanide metformin acts primarily by suppressing endogenous hepatic glucose output with a modest improvement in peripheral insulin sensitivity seen as a secondary effect. The thiazolidinediones are uniquely targeted to insulin resistance. Troglitazone was the first thiazolidinedione, followed by rosiglitazone and pioglitazone. These agents act primarily by decreasing insulin resistance in peripheral tissues, thereby increasing peripheral glucose utilization and lowering circulating glucose concentration; a small reduction in hepatic glucose production may occur. When metformin and troglitazone are combined, they have equal and additive benefits on glycemic control.

Troglitazone: Impact on arteries and endothelial function

Diabetes and insulin resistance are commonly associated with atherosclerosis and with abnormalities of the vascular endothelium. The causal relationship between insulin resistance and atherosclerosis was evident in a 6-month study of the effect of troglitazone on arterial walls in 135 patients with diabetes. Carotid artery intimal-medial thickness (IMT) regressed significantly at 3 and 6 months in the troglitazone group, whereas it progressed in the controls (Figure). Since carotid IMT is a marker of early atherosclerosis, these findings indicate that troglitazone might inhibit early atherosclerosis.

Troglitazone also reduced intimal hyperplasia after coronary stent implantation in 14 patients with type 2 diabetes compared with a control group treated with diet only.

Figure: Effect of troglitazone on carotid intimal medial thickness. Adapted from Minamikawa J et al.

Troglitazone also has favorable effects on endothelium-dependent vasoactivity. Four months of troglitazone therapy significantly improved flow-dependent dilation in 17 patients with impaired glucose tolerance and peripheral vascular disease and in 8 diabetic patients with vasospastic angina, who also had far fewer episodes of angina. Agents targeted at insulin resistance may have a unique advantage over other therapies for diabetes.
Hormone replacement therapy (HRT) relieves menopausal symptoms and protects against osteoporosis, and may prevent coronary heart disease (CHD), the leading cause of death in women. Among its cardioprotective effects, estrogen exerts beneficial effects on lipid metabolism. It also improves coagulation and fibrinolysis and decreases macrophage foam cell formation and insulin resistance, potentially affecting plaque formation and rupture (Table).

Estrogen influences vascular function by modulating vascular tone. Acute infusions of estradiol in coronary arteries in postmenopausal women essentially abolished vasoconstriction. In a long-term study, estradiol significantly increased endothelium-dependent vasodilation in the brachial artery. Combining estradiol with progesterone did not abolish endothelium-dependent vasodilation improvement observed with estradiol alone.

Benefits of HRT on Lipids: PEPI and HERS Trials

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial compared the effects of estrogen and 3 estrogen/progestin regimens on heart disease risk factors in 875 healthy postmenopausal women. With all the regimens LDL-cholesterol (C) decreased and HDL-C increased significantly. Insulin sensitivity improved somewhat. In the Heart and Estrogen/progestin Replacement Study (HERS) in 2763 postmenopausal women with CHD, LDL-C levels decreased and HDL-C rose significantly after 1 year of HRT.

HRT: Anti-atherosclerotic effects in diabetic and nondiabetic women

A large cross-sectional study comparing HRT effects on atherosclerosis in 623 women with and without type 2 diabetes measured carotid artery intimal medial thickness (IMT) as a gauge of atherosclerosis. Current and former HRT users had significantly thinner carotid IMT than nonusers. Women with and without type 2 diabetes had similar beneficial effects with HRT.

HRT and CHD: Current recommendations

Three meta-analyses concluded that HRT decreases CHD risk by 35% to 50%. HRT has also been shown to increase healthy women's life expectancy from 1 to 3 years. The HERS trial, however, found no overall effect on cardiac mortality with HRT in women with CHD. The group taking HRT had more CHD events during the first year and fewer after 4 to 5 years of therapy. Further follow-up is in progress to ascertain the overall effect of initiating HRT in women with CHD.

Recently issued guidelines for preventive cardiology in women suggest that no woman, including those with CHD, should abruptly stop using HRT. Postmenopausal women who already taking HRT at the time of an acute MI may continue therapy. The guidelines stress that risk factor management may be especially important in women with diabetes since it is a powerful threat in women, increasing CHD risk 3- to 7-fold compared with a 2- to 3-fold increase in men.

Table: Effects of estrogen therapy. Adapted from Taskinen M-R.
Coronary angiography has been considered the gold standard for defining coronary artery anatomy, diagnosing disease, and guiding intervention. However, it does not provide functional information and may be misleading regarding the extent and severity of coronary artery disease (CAD). The tomographic (cross-sectional) images of intravascular ultrasound (IVUS) are more sensitive than angiography in detecting atherosclerosis, principally because of the unique capability of IVUS to directly image atherosclerotic plaque.

IVUS studies have demonstrated that atherosclerotic abnormalities are frequently evident in segments with no angiographically apparent lesion. IVUS studies show that by the time the first angiographic lesion is evident, at least 80% of other sites in the coronary circulation meet rigorous criteria for atherosclerosis. Angiographically unrecognized disease has major clinical significance. Numerous studies have shown that two thirds of myocardial infarctions occur at sites of <50% luminal narrowing. The fact that coronary occlusion and myocardial infarction usually involve mild-to-moderate stenoses has advanced the idea that less obstructive plaques are more lipid-rich and vulnerable to rupture.

Vascular remodeling in unstable vs stable angina

Remodeling describes the changes that occur in the elastic external membrane (EEM) during the development of atherosclerosis, most commonly an enlargement in the EEM that preserves lumen size during disease progression. Studies of lesions in patients with stable and unstable angina reveal differences in vessel wall remodeling associated with acute coronary events. In stable angina most lesions exhibit negative remodeling, contributing to an increase in stenotic severity. In unstable angina, most lesions exhibit positive remodeling, in which the EEM adapts outwardly. This results in large plaques, but protects against stenosis (Figure).

In a study of patients with stable angina versus unstable angina, plaque area and the extent of remodeling were significantly greater in the unstable lesions in vessels of similar size and diameter. The bulky remodeled atheroma seem to be more vulnerable to plaque rupture and acute coronary syndromes. Thus, while positive remodeling protects against angina, it increases the risk of sudden death.

Angiography misses benefits of lipid lowering

Despite sharp reductions in cardiac events with even modest lipid reductions, the angiographic changes are often negligible. Nevertheless, IVUS suggests that removal of lipid material from the vessel wall may allow atheroma regression without changing the lumen size. Thus plaque volume is reduced, and the plaque becomes more fibrous (stable) and less likely to rupture. These quantitative and qualitative changes in plaque may occur with no impact on lumen size.

"IVUS images have greatly increased understanding of the anatomy and pathophysiology of coronary disease. For the practicing physician, IVUS reemphasizes the importance of maintaining an aggressive approach to risk factor reduction, particularly reduction in lipid levels."
References

The fibrinolytic system: A therapeutic target in cardiovascular dysmetabolic syndrome

Hypertension: Accelerating atherosclerotic disease
Selected Readings

Review of recent clinical trials to improve endothelial function

Aggressive vs moderate approach to treating dyslipidemia


New vascular targets in treating diabetes


Glucose control and insulin resistance: New mechanistic insights


Update on hormone replacement therapy and heart disease prevention in women


Intravascular ultrasound and angioplasty: Exploring therapeutic options


For more information about the Vascular Biology Working Group, go to www.vbwg.org.