Aspects of Blood Pressure, Lipid, and Glycemic Treatment

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Blood pressure treatment

William Cushman described the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which had a total of 33,357 hypertensive participants, 36% of whom had diabetes, making it the largest study of blood pressure treatment in diabetes (1). Interestingly, 60% of the population studied satisfied criteria for the metabolic syndrome. In both the diabetic and nondiabetic subgroups, there was no difference in coronary heart disease (CHD) events or mortality between patients randomized to chlorthalidone, amlodipine, and lisinopril. Congestive heart failure (CHF) was less common with chlorthalidone than with the other agents. For those with fasting glucose <126 mg/dl at baseline, the mean glucose was 93 mg/dl at baseline, with levels increasing to 104 mg/dl with chlorthalidone, 103 mg/dl with amlodipine, and 101 mg/dl with lisinopril at 4 years. Similarly, diabetes incidence was highest with chlorthalidone at 11.6% vs. 9.8% with amlodipine and 8.1% with lisinopril. Including those persons who developed diabetes, and those with fasting glucose >126 mg/dl who had unrecognized diabetes, 39, 40, and 39% of persons in the three groups actually had diabetes. In each group, 4% had impaired fasting glucose (IFG) at levels of 110–125 mg/dl. The diabetic participants had 36% CVD prevalence, as opposed to 62% of the IFG and nondiabetic groups, based on the differing entry criteria for those with and without diabetes. Initial fasting glucose levels were 169, 116, and 91 mg/dl in the respective groups. Lisinopril did not lower systolic blood pressure as effectively as the two other agents, although it affected diastolic blood pressure similarly. Among persons with diabetes, at 2 years fasting blood glucose decreased 3 and 2 mg/dl with amlodipine and lisinopril, respectively, while increasing 6 mg/dl with chlorthalidone. In the IFG group, mean blood glucose increased from 116 mg/dl at baseline to 130, 123, and 116 mg/dl at 2 years and to 129, 130, and 117 mg/dl at 4 years, with chlorthalidone, amlodipine, and lisinopril, respectively. The incidences of diabetes among those with IFG were 44, 35, and 27% at 2 years and 39, 38, and 29% at 4 years, so that lisinopril was associated with a 25% lower relative risk of diabetes in this subset. For those with normal glucose at baseline, at both 2 and 4 years glucose levels were significantly higher with chlorthalidone, with higher diabetes incidence at both time points. For patients with IFG, amlodipine was associated with significantly worse outcome than with either chlorthalidone or lisinopril, with a 90% greater CVD risk and 40% higher CHF risk, and the CHF risk was 17% higher with lisinopril than with chlorthalidone. In persons with diabetes, no significant difference was seen between agents in CHD, all-cause mortality, stroke, or combined CVD. Cumulative mortality for hospitalized CHF patients was 50% at 5 years regardless of which drug was used, a prevalence that was five times greater than that in patients without CHF. Interestingly, and perhaps contributing to the unexpectedly unfavorable outcome with lisinopril, 29% of patients discontinued this agent at 5 years, as opposed to 20% of those treated with chlorthalidone and amlodipine.

John M. Lachin (Rockville, MD) discussed the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up of ~1,300 of the 1,441 persons enrolled in the Diabetes Control and Complications Trial (DCCT) for an additional 8 years after the mean of 6.5 years in the DCCT. During the trial, the control and intervention groups had mean HbA1c of ~9 vs. 7%, with retinopathy progressing in 15 vs. 3% at 4 years and a 76% decrease in risk over 9 years among those in the primary intervention. The risk of retinopathy was greatest among those entering with the highest HbA1c, and longest duration of diabetes, both among conventional and intensive treatment groups (2). The effects of glucose increase were long lasting, with each year of diabetes having greatest effect early in the course of the disease. The DCCT was closed in 1993, patients were enrolled in EDIC in 1994, and, after 1 year, HbA1c had fallen to 8.2% in the previous control group while rising to 8% in the previous intensive treatment group. However, after adjusting for previous retinopathy, 63% retinopathy risk reduction was seen in the latter group. For each 1% higher HbA1c during the DCCT, the risk of retinopathy progression during EDIC was 2.67-fold greater. For normoalbuminuric persons, the risk of new clinical albuminuria was 83% lower among those who had been in the intensively treated group. This phenomenon of “metabolic memory” suggests that a year of hyperglycemia experienced earlier in the course of a patient’s diabetes has greater effect earlier than one experienced later. Overall, the mean HbA1c during the DCCT explained 94–98% of renal and retinal complications during EDIC.

Based on these studies, Lachin stated, a person whose HbA1c was 7% during the last 4 years of the DCCT but 9% thereafter would have a 1% annual risk of retinopathy progression, whereas a person whose HbA1c was 9% for the first 4 years and...
then 7% for the next 4 years would have a 4.3% annual risk. Comparing the same glycemic control parameters, a person who had nonproliferative retinopathy at baseline would have a 14.4 vs. 3.6% annual risk, further suggesting the importance of earlier treatment of diabetes. A skin biopsy study near the conclusion of the DCCT in 216 persons showed that the risk of microvascular complications was associated with the presence of collagen advanced glycation end products independent of the HbA1c level (3). Thus, glycation and glycoxidation may contribute to the phenomenon.

**Hyperglycemia in critical illness**

Abbas Kitabchi (Memphis, TN) discussed the association of hyperglycemia with critical illness in a study of 1,886 patients admitted to hospital, of whom 223 were newly found to be hyperglycemic, 465 were known to have diabetes, and 1,168 were normoglycemic. Of the former group, 29% required intensive care unit (ICU) admission compared with 14 and 9% of the latter two groups (4). Respective mortality rates were 16, 3, and 1.7%, with non-ICU mortality 10, 1.7, and 0.9%. Infection was the cause of death in 33, 27, and 20% of the respective groups, while 28, 53, and 50% were caused by CVD.

The pathophysiology of stress hyperglycemia involves increased catecholamines, glucagon, and cortisol, resulting in decreased effective insulin activity, increased glycogenolysis, gluconeogenesis, and free fatty acid (FFA) levels, and decreased glucose utilization. In persons with insulin-requiring diabetes, the biochemical responses seen during insulin pump withdrawal with attendant ketogenesis are of increases in FFA, cortisol, glucagon, and norepinephrine (5). Cytokine levels increase in patients with ketoacidosis and hyperglycemia. Leukocyte counts increase with ketoacidosis, with a high level of the CD69 growth receptor on both CD4 and CD8 T-cells, improving with resolution of the hyperglycemia. Flow cytometry T-cell subset analysis suggests that these usually insulin-insensitive cells, when activated by high glucose, develop insulin, IGF-1, and interleukin-2 receptors, suggesting that acutely, hyperglycemia increases certain immune responses, perhaps by causing oxidative stress and lipid peroxidation.

Greet Van den Berghe (Leuven, Belgium) discussed blood glucose control in the ICU. By definition, a critically ill patient is dependent on support for survival. In her unit, 36% of ICU patients require such support for >5 days. High IGFBP-1, which is associated with relative insulin deficiency, discriminates survivors from nonsurvivors even weeks before death (6). Hyperglycemia is common in ICU patients, reflects severity of illness, is caused by insulin resistance in liver and muscle, and in a sense is adaptive in providing glucose for brain, red cells, and wounds. In the past, she noted, treatment has only been utilized when blood glucose exceeds 215 mg/dl (12 mmol/l). Her group hypothesized, however, that hyperglycemia, with glucose levels exceeding 110 mg/dl, contributes to ICU complications. They randomized all mechanically ventilated adults admitted to the ICU to conventional insulin for glucose levels >155 mg/dl or intensive insulin for glucose >110 mg/dl (7). The study was superimposed on a feeding schedule gradually increasing to 25 kcal·kg⁻¹·day⁻¹ after 7 days. Insulin was administered via continuous pump with glucose testing every 1–4 h and doses were adjusted by ICU nurses and a study physician not involved in decision making. There was a history of diabetes in 13% of patients, and 12% had glucose >200 on admission, with incomplete overlap between the two groups. The control group had a mean glucose of 150 mg/dl, whereas the intensive group had levels around 100 mg/dl and required insulin infusion at a rate of 3–4 units/h. Mortality was 8 vs. 4.6% for conventional versus intensive treatment; levels were equal in the two groups at day 5 but were 20.2 vs. 10.6% for persons requiring long ICU stays. Of the 204 with a previous diabetes history, 5.8 vs. 3.9% mortality was seen, again with effect in the long-stay group. “We prevent death in the more chronic phase by intervening from the start.” The cause of death particularly influenced was multiple-organ failure with sepsis, which decreased by 46%. Prolonged use of antibiotics, prolonged mechanical ventilation, and critical illness polymyopathy decreased. Renal failure decreased from 23.9 to 14.9%. Brief hypoglycemia was seen in 5.2 vs. 0.8%, never associated with critical symptoms, and occurred in the “stable phase” and usually when the insulin infusion was not turned down with interruption in feeding. Van den Berghe noted that both insulin and metabolic control were positive risk factors, suggesting that insulin per se may or may not be directly protective. There was, however, a stepwise increase in adverse outcome with increasing glucose levels.

IGFBP-1 does not change with insulin administration, but persons with high IGFBP-1 do have increased mortality. Hepatic phosphoenolpyruvate carboxykinase gene expression is not affected in models of critical illness, suggesting that the effect of insulin treatment did not involve the liver, while muscle levels of the glucose transporter GLUT-4 are affected, suggesting a peripheral action. Van den Berghe noted that there is a linear relationship between serum triglyceride and mortality and an association between low LDL and increased mortality risk. In multivariate analysis, LDL and HDL in a “toxic” low range seem to be the major risk factors. Both are benefited by insulin treatment. Insulin treatment is also associated with suppression of C-reactive protein (CRP) and mannose-binding lectin (8). Van den Berghe pointed out that the cost of 1 day in the ICU is ~$1,400, so that the 3-day mean savings of an ICU stay led to a large cost reduction.

Miles Fisher (Glasgow, Scotland) discussed glucose control in the Coronary Care Unit. Diabetes is associated with premature cardiovascular death, “and nowhere is this more clear than when diabetic patients have a myocardial infarction.” More silent myocardial infarction, delay in receiving treatment, more frequent CHF, cardiogenic shock, rupture, and reinfarction occur, suggesting that treatment is crucial. In the U.K. Prospective Diabetes Study, CHD was associated with raised LDL and low HDL cholesterol, HbA₁c, systolic blood pressure, and cigarette use. Preinfarction factors include distal vessel CHD, diabetic cardiomyopathy, autonomic neuropathy, and impaired fibrinolysis, while there are also acute changes in myocardial metabolism, suggesting a role of acute intervention to change from FFAs to glucose utilization. Glucose requires less oxygen, and FFAs may be arrhythmogenic. Low-dose parenteral insulin appears to be safe (9–11), but studies performed in the 1980s had poor design with low numbers of patients, although one showed mortality to be decreased from 42 to 17% in comparison with a historical control. A subsequent Scottish study showed no dif-
ference in mortality or arrhythmia but was felt to be underpowered (12). The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study began with a feasibility analysis of 327 persons with diabetes and myocardial infarction randomized to insulin versus conventional treatment. No differences in tachyarrhythmia or ischemic events were seen despite ~15% of patients having hypoglycemia (13). In the full subsequent study in 19 Swedish hospitals, insulin was administered according to a defined protocol, initially at a rate of 4.8 units/h, with 1,240 patients screened and 620 randomized (314 control and 306 intensively treated persons with diabetes and myocardial infarction) (14). There were some imbalances between the groups, with 36 vs. 40% having prior beta-blocker treatment and 15 vs. 10% not previously known to have diabetes, but Fisher suggested that mismatching at baseline was probably not the cause of the decrease seen in mortality at 1 and 5 years in the intensively treated group. The potential causes of the benefit may have been from the initial intravenous insulin, from the continued treatment with subcutaneous insulin, or from the withdrawal of previously given agents that may have had an adverse effect on the heart. Intravenous insulin decreases FFA levels, which improve oxygen requirements of ischemic tissues. Insulin also promotes potassium entry into cells, is anti-inflammatory, has antithrombotic effects, and reduces reperfusion injury. A myocardial infarction relates a state of "cytokine storm" with massive release of substances such as tumor necrosis factor (TNF)-alpha that can decrease myocardial contractility, induce apoptosis, and have prothrombotic effects. In a smaller postmyocardial infarction study carried out with a protocol similar to that in the DIGAMI, intravenous insulin decreased fibrinogen and plasminogen activator inhibitor 1 levels, as compared with the increases seen in control subjects (15). Reperfusion injury involves both necrosis and apoptosis, with pathways including phosphatidylinositol 3-kinase, Akt, and p70S6, potentially modified by insulin administration. The potential exists that the benefit in DIGAMI was caused by withdrawal of sulfonylureas rather than by the administration of insulin per se. Ischemic preconditioning refers to the phenomenon of greater vasodilation to a second rather than a first episode of decreased coronary perfusion, which may improve outcome in acute myocardial infarction. This appears to be blocked by sulfonylureas such as glyburide. There is, however, evidence in nondiabetic persons that infusion of glucose, insulin, and potassium improves mortality after myocardial infarction by 28% in a meta-analysis of 15 studies, so that it appears likely that the insulin effect is real. The DIGAMI-2 study, which is being carried out in Sweden, Norway, Finland, and Scotland, will randomize 3,000 patients to intravenous plus subcutaneous insulin, to intravenous insulin followed by conventional treatment, or to conventional treatment alone, with results due in 2004.

Dyslipidemia

Alan Chait (Seattle, WA) gave the Edwin Bierman lecture on lipoproteins "beyond the plasma compartment," an interest that began when he and Bierman studied the interaction of plasma lipoproteins with the arterial wall. Diabetic dyslipidemia is characterized in the plasma compartment by normal to borderline LDL cholesterol levels with small dense particles that are associated with increased apolipoprotein (apo)B, reduced HDL, and high triglyceride levels; increased VLDL of altered composition and increased levels of remnant particles; and abnormal HDL2 particles. In the arterial wall, lipoproteins are excessively retained and oxidized, leading to the development of atherosclerosis. Lipoproteins interact with proteoglycans in the arterial wall, with retention and subsequent modification, as by oxidation, leading to foam cell formation. The positively charged apoB and apoE interact with negatively charged carboxylic acid residues or sulfate groups on the side chains of the proteoglycans. Specific sites on apoB are important for binding with proteoglycans, as studies have suggested that mutated LDLs with defective proteoglycans binding lead to less atherosclerosis at a given LDL level.

There are four major extracellular proteoglycan classes, versican, with 15–20 side chains, perimac, a heparin sulfate–rich proteoglycan, bglycan, and decorin. Biglycan, although quantitatively less than the other classes, is associated with apolipoproteins in human atheromas. In diabetes and the metabolic syndrome, CVD risk is increased in association with hypertriglyceridemia. Chait noted that the content of apoCIII, which does not have positively charged residues, is strongly associated with proteoglycans binding, suggesting that in persons with insulin resistance, these particles have altered surface conformation of apoB and apoE, leading to increased binding. Furthermore, small dense LDLs have a number of atherogenic features, including greater penetration of the endothelial barrier, increased retention by vascular matrix, increased susceptibility to oxidation, and association with atherogenic lipoprotein phenotype. These particles also show greater biglycan binding.

Chait showed interesting data suggesting "some HDL might actually be bad for you." ApoA1 shows colocalization to biglycan with apoB and apoE, a finding that has been noted a number of times over the past several decades and, in the mouse, it is the major lipoprotein in atheromas. HDL containing apoE shows particularly great binding. Serum amyloid A (SAA) is an inflammatory peptide synthesized by the liver in response to stimuli such as interleukin-1 and -6 and TNF-alpha, increasing in parallel with CRP in humans. As CRP is not present in mice, the effect of SAA can be studied in isolation in this species. SAA is primarily associated with HDL and has a positively charged domain that may lead to proteoglycans binding. In a cholesterol- and fat-fed LDL receptor–deficient mouse model, SAA levels are high and correlate with increased atherosclerosis, suggesting that it may be a mediator. In diabetes, CRP and SAA levels increase with increasing insulin resistance. In insulin-sensitive persons, both markers increase with cholesterol feeding but, in insulin-resistant persons, levels are increased irrespective of dietary cholesterol. Chait hypothesized that SAA targets a subset of apoE-containing HDL particles, leading to atherosclerosis.

There are a number of modifications of extracellular proteoglycans that can increase LDL retention. Glucose increases and thiazolidinediones inhibit proteoglycans synthesis. Oxidized LDLs lengthen the proteoglycans side chains, increasing LDL binding. However, oxidation of LDL blocks the positive charges on apoB and apoE and reduces proteoglycans adhesion, although other matrix components such as fibronectin and laminin bind avidly to oxidized LDL, promoting foam cell formation. Thus, oxidized lipoproteins
exert a variety of toxic effects leading to atherosclerosis. Oxidized LDL is relevant to diabetes, with increased oxidation susceptibility of small dense LDL and increased levels of LDL oxidation markers. “It’s just that vitamin E is not the way to go,” Chait concluded, suggesting that “we need to get smarter about antioxidant strategies.”

Christie Ballantyne (Houston, TX) discussed transplantation dyslipidemia, focusing on persons with renal transplants. There are specific increases in CVD risk because of proteinuria and increased cytokine levels, particularly in persons with diabetes, who also have increased levels of risk factors before the transplant. Cyclosporin increases total and LDL cholesterol by both increasing production and decreasing degradation, and it decreases plasma lipoprotein lipase activity—effects not seen with tacrolimus. Sirolimus leads to marked dose-related increase in triglyceride levels, although it does not show adverse interaction with statins. Prednisone treatment also has hyperlipidemic effects. Not only do the immunosuppressive drugs raise lipids, but hyperlipidemia may decrease the efficacy of these drugs, as they are highly lipophilic and bind to circulating lipids, perhaps causing toxicity more frequently in persons with low lipid levels. Statin therapy may therefore increase efficacy and toxicity of these agents. Ballantyne noted that there are a number of cytokine effects on lipoproteins, including modifications of LDL particles, with TNF-α increasing triglyceride and SAA decreasing HDL cholesterol.

Clinically, statin treatment improves survival in the relatively small reported heart transplant studies. Its benefit is seen earlier and appears to be greater than that in nontransplant populations. Recently, the randomized controlled ALERT (Assessment of Lescol in Renal Transplantation) trial studied 2,102 renal transplant recipients on cyclosporine. The subjects were aged 30–75 years with 4–9 mmol/l cholesterol treated with 40 or 80 mg fluvastatin or placebo for 5.1 years, resulting in a 32% LDL reduction. Although coronary intervention procedures and total mortality did not significantly decrease, CVD mortality and myocardial infarction decreased 35% (16). There were minimal adverse effects, given the low drug interaction profile with this agent versus other statins, suggesting this to be a particularly useful agent in persons receiving immunosuppressive agents. No benefit in graft rejection was seen, in contrast with earlier reports from noncontrolled trials.

Ballantyne briefly discussed other classes of lipid-lowering agents. Bile acid binding resins may interfere with absorption of immunosuppressive agents. Niacin may increase glucose levels. Fibrates, particularly gemfibrozil, may cause myopathy in combination treatment with statins, an effect particularly seen with lovastatin. Ezetimibe appears safe, but few studies are available. ω-3 fatty acids appear to be safe and can be used in combination with statins. Ballantyne suggested that, to avoid toxicity, treatment to the Adult Treatment Panel-III (ATP-III) target level may not be desirable.

Robert Toto (Dallas, TX) discussed dyslipidemia in renal failure, noting that chronic kidney disease is a risk factor for cardiovascular mortality, that dyslipidemia is linked to both proteinuria and renal damage, and that treatment has not been proven effective in this population. In 2000, 280,000 persons in the U.S. were on dialysis, with an anticipated increase in 2010 to 520,000 persons, of whom half will have diabetes. Cardiovascular death is the most common cause of mortality, with event rates markedly higher than in the non–end-stage renal disease population, and there are several hundred-fold increases in persons under age 50. Cardiovascular risk increases before need for dialysis. In the HOPE (Heart Outcomes Prevention Evaluation) study, controlling for major risk factors, creatinine ≥1.4 mg/dl was associated with higher myocardial infarction and cardiovascular mortality rates. Renal injury causes dyslipidemia and may itself be worsened by lipid abnormalities, perhaps by contributing to ischemic renal damage. In the Modification of Diet in Renal Disease study of persons with established chronic renal failure, low HDL predicted renal disease progression. Proteinuria is associated with increased LDL production and decreased removal, and CVD rates are increased in primary nephrotic syndrome. The major lipoprotein abnormalities are of increased VLDL remnants, increased lipoprotein(a), low HDL cholesterol, and abnormal particle composition with oxidized and carbamylated LDL, increased VLDL apoCIII, and increased small dense LDL, all atherogenic abnormalities. Some congenital lipid abnormalities, such as Fabry’s disease and “fish eye” disease are associated with development of renal disease. Persons who develop renal disease appear to have dyslipidemia, particularly with increased triglyceride levels, and low HDL also appears to be a predictor, suggesting underlying metabolic syndrome. ACE inhibitors and ARBs decrease proteinuria, and there is evidence that ACE inhibitors may decrease LDL cholesterol levels. Toto referred to a meta-analysis showing a 1.9 ml·min⁻¹·year⁻¹ lesser decrease in gomerular filtration rate with lipid treatment. Statins are effective in nephrotic syndrome, persons with diabetic nephropathy, and persons on dialysis and are generally safe and well tolerated with low incidence of myopathy. There is evidence suggesting that lipid treatment may be associated with regression of microalbuminuria among patients with type 1 diabetes (17). Statin treatment has been associated with improved survival in observational studies of dialysis populations.

Eliot Brinton (Phoenix, AZ) discussed the treatment of hypertriglyceridemia and low HDL cholesterol. Most large studies show strong a relationship of these lipid variables, particularly HDL, to CHD, but HDL “has lagged as a therapeutic target,” in part because of lack of available agents. The “pendulum [is] swinging toward HDL,” Brinton said, because statins do not prevent the majority of events and because new HDL-raising agents, which may have anti-inflammatory and cholesterol-efflux effects, are becoming available. Causes of low HDL include hypertriglyceridemia, hyperglycemia, obesity, high carbohydrate intake, cigarette smoking, and progestins. Familial hypoalphalipoproteinemia, although uncommon, may be a factor. Niacin is probably the best HDL-raising agent, and fibrates, statins, estrogen, and alcohol also raise levels. Niacin’s favorable effects on total cholesterol and LDL particle size may be particularly beneficial. Fenofibrate and gemfibrozil actually have only modest effects, even with dramatic triglyceride lowering. Among statins, rosuvastatin has a particularly good effect, atorvastatin appears to show an undesirable negative dose response, and pravastatin and fluvastatin appear to have positive dose-response effects.

Studies with niacin include the Coronary Drug Project, which showed event
and mortality reduction on 15-year follow-up (18), and a simvastatin plus niacin trial showing dramatic reduction in events, interestingly with antioxidant vitamins appearing to lessen HDL and event benefit (19). In the AF CAPS/TexCAPS studies, persons in the lowest HDL category (<40 mg/dl) had the greatest degree of event reduction with fluvastatin (21), and that those with HDL <39 mg/dl and triglyceride ≥160 mg/dl have greatest benefit from simvastatin (22). Among persons with low HDL and LDL cholesterol, an increase in HDL is a better predictor of outcome than the triglyceride decrease (23), and those with lower HDL have the greatest event reduction with gemfibrozil (24).

Brinton noted that the ATP-III recommendations of the National Cholesterol Education Program “doesn’t really say much,” giving little guidance to increasing HDL. He suggests HDL goals of 40 and 50 mg/dl in men and in women. Lifestyle change and niacin are the most effective measures, and fibrates and statins are additional medication options for secondary prevention.

Triglyceride levels are independent risk factors in many studies, although given their negative relationship to HDL levels, this is difficult to assess, and the variability of fasting triglyceride in a given person may make it “drop out” in mathematical analysis. Triglycerides may have direct prothrombotic effect and may be a marker of other abnormalities such as hyperglycemia. There may be greater risk of hypertriglyceridemia in women than in men, particularly with diabetes or insulin resistance. The DIAS (Diabetes Atherosclerosis Intervention Study) showed angiographic evidence of benefit of fenofibrate in persons with type 2 diabetes (25). Brinton pointed out the need to look for secondary factors, including alcohol use, in persons with hypertriglyceridemia; the need to decrease dietary fat and carbohydrate intake; the effects of medications, particularly estrogen, glucocorticoids, and HIV drugs; the benefits of improving glycemic control, weight loss, and exercise; and the possible benefit of insulin-sensitizer treatment. The ATP-III suggests fibrates, nicotinic acid, statins, and ω-3 fatty acids in high doses. Brinton recommended a treatment goal of 150 mg/dl and stated that treatment was certainly needed for persons with baseline levels >500 mg/dl. The use of non-HDL cholesterol as a target is recommended by ATP-III with hypertriglyceridemia.

Although small dense LDL is associated with hypertriglyceridemia and low HDL, it is uncertain as to whether one should measure particle size, although commercial methods are now available.

“We’re going to underestimate the problem if we don’t know that the patient has small dense LDL,” Brinton pointed out, and these persons need aggressive LDL lowering with statins or niacin and perhaps with agents to increase LDL size, although “we don’t know” the optimal treatment.

References

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