

Dyslipidemia and the Metabolic Syndrome

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This is the third in a series of articles on presentations at the American Diabetes Association Annual Meeting, Orlando, Florida, 4–8 June 2004.

Lipid-related epidemiology

A number of presentations at the June American Diabetes Association (ADA) meeting addressed aspects of lipid therapy of persons with diabetes. Brown et al. (abstract 929) reported the correlation between fasting lipids and HbA_{1c} in 11,938 persons with diabetes in the Kaiser Permanente Northwest population. Comparing persons with no, one, and two high-cardiovascular disease (CVD) risk lipid abnormalities, HbA_{1c} was 7.3, 7.5, and 7.9%, triglycerides 150, 210, and 381 mg/dl, and HDL 54, 40, and 37 mg/dl, respectively, suggesting association of poorer glycemic control with dyslipidemia in type 2 diabetes. Pladevall et al. (abstract 948) described trends in the management of dyslipidemia in patients with diabetes using a managed care database of 9,642 persons, 6,751 of whom were followed from 1997 to 2001. Lipid testing was performed in 37, 44, 51, 55, and 6% in 1997, 1998, 1999, 2000, and 2001, respectively. During this period, 19, 23, 28, 33, and 41% of patients were prescribed a lipid-lowering agent and the LDL cholesterol goal of <100 mg/dl was attained by 22%, 27%, 32%, 34%, and 37%, respectively, suggesting that important improvement has been made, although there is a great deal yet to be done in lipid treatment of persons with diabetes in the U.S.

LDL-targeted therapy

Ronald Goldberg (Miami, FL) discussed LDL-targeted therapy, addressing the re-

lationship between LDL cholesterol and CVD in diabetes, lessons learned from statin trials in diabetes, current guidelines for LDL-targeted therapy, and new data regarding the question of more rather than less statin, as well as special subgroups and obstacles to achieving goals. In the UKPDS (U.K. Prospective Diabetes Study), LDL levels were similar to those of persons without diabetes in men and slightly elevated in women (1), but with LDL as the most powerful CVD risk factor, while in the MRFIT (Multiple Risk Factor Intervention Trial), serum cholesterol and CVD mortality showed similar relation in men with and without diabetes, but with rates “vastly” increased in the former (2).

LDL particles enter the subendothelial space and are oxidized with subsequent uptake by macrophages, leading to their activation and to foam cell development, thereby beginning the process of atherosclerotic plaque development that leads to CVD events. Additional factors associated with diabetes driving the atherosclerotic process include oxidative stress, inflammation, and cytokine excess, leading Goldberg to suggest an approach of LDL lowering for persons with diabetes beyond the degree required in nondiabetic persons. He noted that the Heart Protection Study (HPS) diabetic subgroup of 5,983 men and women with baseline LDL cholesterol of 125 mg/dl showed a 22–25% reduction in CVD end points not affected by sex, age, or HbA_{1c}, with similar benefit among persons with and without known CHD. Those with LDL >116 or <116 mg/dl had a decrease in events of 20 and 27%, respectively (3). Collaborative Atorvastatin Diabetes Study (CARDS) (discussed below) also showed

similar benefit for diabetic persons with LDL above and below the mean baseline level of 120 mg/dl. An important question is the appropriate intensity of statin treatment. In the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial, intravascular ultrasound was used to study coronary artery plaque progression following an 18-month period of treatment with 40 mg pravastatin versus 80 mg atorvastatin daily in 634 persons with CHD, showing 2.7% increase vs. 0.4% decrease, respectively (4). The PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study of 4,162 persons showed, over 30 months, a 16% lower CVD event rate with 80 mg atorvastatin (5). Goldberg suggested, “Many of us who treat very high risk persons are going to feel the pressure to maximize treatment.”

In the HPS, persons who appeared to have type 1 diabetes showed evidence of parallel benefit from statin therapy, and there is evidence that CVD in persons with type 1 diabetes begins around age 40 years, suggesting that statins should be initiated by age 30 in this group (6). Similarly, younger persons with type 2 diabetes have more markedly increased relative CVD risk than older type 2 diabetic persons (7), implying that early initiation of statins is appropriate for all young persons with diabetes when LDL levels are even mildly elevated. Another important group is that of persons with renal insufficiency. In the HPS, there were 310 diabetic persons with elevated creatinine; the event rate was almost twice that of those with normal creatinine levels, suggesting this to be a group particularly benefiting from treatment. Goldberg suggested that there is “unwarranted fear of adverse events” and that statins should be increased appropriately and combinations of statins with ezetimibe, bile sequestrants, high-dose niacin, and phytosterol supplements be more widely utilized.

Several studies presented at the meeting reviewed effects of ezetimibe. Denke et al. (abstract 517) reported the effect of addition of ezetimibe to statin therapy. Among persons with diabetes, 739 receiving the combination had a 25% greater

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Abbreviations: ADA, American Diabetes Association; apo, apolipoprotein; CARDS, Collaborative Atorvastatin Diabetes Study; CETP, cholesterol ester transfer protein; CRP, C-reactive protein; CVD, cardiovascular disease; FFA, free fatty acid; HPS, Heart Protection Study; IL, interleukin; LCAT, lecithin-cholesterol acyl transferase; LPL, lipoprotein lipase; SD-LDL, small dense LDL; TNF, tumor necrosis factor.

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Table 1—Effects of single and combination treatments for individuals with diabetes

	Fibrate	Thiazolidinedione	Statin	Niacin	Fenofibrate plus statin	Niacin plus statin
Triglycerides	2+	1+	2+	3+	2+	3+
HDL cholesterol	1–2+	1+	0	4+	2+	3+
HDL2	?	1–2+	4+	4+	?	3+
LDL size	?	1+	1+	3+	?	3+
SD-LDL	3+	1–2+	3+	3+	3+	3+

fall in LDL cholesterol than the 387 subjects receiving statin alone, while among persons with the metabolic syndrome, 1,167 receiving the combination had a 24% greater fall than 572 receiving statin alone. In a small study, Wolf and King (abstract 637) compared 61 diabetic subjects given a double dose of atorvastatin dose with 25 subjects who were also given ezetimibe. The results showed a 20 vs. 45% fall in LDL cholesterol and a 13% increase vs. 16% decrease in triglyceride levels. Hood (abstract 939) reported the effects of 10 mg ezetimibe daily in 42 persons with type 2 diabetes, showing 32 and 11% decreases in LDL cholesterol and triglycerides from 127 and 201 mg/dl, respectively. Although there was no change in HDL in the overall group, those persons with HDL <40 mg/dl had an 11% increase in levels, suggesting a role in the treatment of diabetic dyslipidemia. McKenney et al. (abstract 944) reported the effects of 20 mg simvastatin alone vs. 20 mg simvastatin plus 10 mg ezetimibe daily in 113 vs. 60 persons with diabetes, showing falls in LDL from 166 and 162 mg/dl, respectively, by 39 vs. 53%.

CARDS

Helen Colhoun (London, U.K.) presented the results of the CARDS (8) at a symposium describing “late-breaking studies.” The study was carried out at 132 centers in the U.K. and Ireland to address the role of lipid lowering with 10 mg atorvastatin daily versus placebo in 2,838 (1,428 vs. 1,410) patients with type 2 diabetes and mean HbA_{1c} 7.9% with LDL ≤160 mg/dl and triglycerides ≤600 mg/dl, without a history of coronary, cerebrovascular, or severe peripheral vascular disease and with cigarette use (in 22%), microalbuminuria (in 15%), hypertension (in 84%), and/or retinopathy (in 30%). Mean LDL cholesterol decreased 46 mg/dl from a baseline of 119 mg/dl, and triglycerides decreased 35 mg/dl from 150 mg/dl, with

80–90% of patients showing LDL cholesterol <100 mg/dl in the active therapy group, whereas there was no change in lipid levels in the placebo group, although by the end of 4 years, 15% of these patients were receiving lipid-lowering treatment and 22% of those in the intervention group had discontinued atorvastatin.

Comparing the placebo and atorvastatin groups, there were 189 vs. 134 total CVD events (a 32% risk reduction). There were 127 vs. 83 acute coronary events, coronary revascularizations, or stroke (a 37% decrease). Fatal and nonfatal myocardial infarction occurred in 20 vs. 8 and 41 vs. 25 persons, respectively, coronary artery bypass surgery was performed in 34 vs. 24, and stroke occurred in 39 vs. 21. Benefit was seen for persons with LDL cholesterol above and below 120 mg/dl, although analysis was not reported at the LDL threshold of 100 mg/dl. Death occurred in 82 vs. 61 persons, a 27% risk reduction of borderline statistical significance (*P* = 0.059). Colhoun concluded that statin treatment is safe and efficacious, suggesting that there is no justification for an LDL threshold, but rather that overall CVD risk should be the determining factor in which patients should receive this treatment, leading to the question as to whether any patients with type 2 diabetes are at sufficiently low risk that statins should not be used.

HDL-targeted therapy

M. Arthur Charles (Tustin, CA) discussed HDL-targeted therapy, reviewing the function of HDL and the effects of various treatment approaches. Low HDL cholesterol is the most common lipid abnormality, underlying CHD, metabolic syndrome, and dysglycemia, with additive adverse effect to elevations in LDL. Recent studies with infusion of apolipoprotein (apo)A1 Milano further suggest the potential for benefit of HDL-raising treatment (9), with Charles suggesting

that both HDL-raising and LDL-lowering treatments offer up to a 30% reduction in CVD events and that there may be as much as an 80% reduction in events by addressing both abnormalities. Although niacin is not widely used clinically, there has been evidence of benefit of treatment with this agent for more than a decade.

HDL is comprised of a heterogeneous set of molecules, mediating reverse cholesterol transport, involving proteins including apoA1, lecithin-cholesterol acyl transferase (LCAT), cholesterol ester transfer protein (CETP), and ATP-binding cassette transporter A1. HDL has antioxidant effects mediated by apoA1, paraoxonases, LCAT, and platelet-activating factor; anti-inflammatory effects, in part by blocking adhesion of monocytes; endothelium-stabilizing effects by promoting nitric oxide (NO) synthesis, and actions reducing platelet aggregation and promoting fibrinolysis. Nascent HDL particles contain two apoA1 molecules, phospholipids and triglycerides, and attach to tissues that express ATP-binding cassette transporter A1, gaining free cholesterol. In the presence of LCAT, HDL cholesterol can be esterified, producing larger molecules that may be subsequently modified by paraoxonases. CETP interacts with this particle and with LDL and VLDL1 particles, with cholesterol ester transferring to LDL particles both directly and indirectly via VLDL. Cholesterol ester from HDL is taken up by the liver directly by hepatic HDL holoparticle receptors and indirectly via the LDL receptor and by scavenger receptor class B, type I, with cholesterol ester then excreted in bile. In persons with type 2 diabetes, there are increased levels of VLDL1, with its triglycerides being taken up by HDL2 particles, which are then hydrolyzed via hepatic lipase, and the smaller HDL particles then potentially excreted in the urine. CETP also can transfer triglycerides from VLDL via lipoprotein lipase (LPL) to an LDL subspecies that is acted on by hepatic lipase to produce small dense LDL (SD-LDL) particles.

Charles discussed a variety of approaches to monotherapy and combination treatment of low HDL cholesterol for persons with diabetes (Table 1). Statins may increase HDL2 levels and reduce SD-LDL, and combination fenofibrate-statin treatment markedly decreases apoB. LDL size itself, Charles stated, is misleading, with the SD-LDL cholesterol mass a better

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therapeutic target. Niacin increases LDL size, for example, while statins lower LDL mass, so that combined use of both has optimal effect. Between 5 and 15% of persons do not respond to niacin, perhaps related to genetic differences. Reviewing a study from his group of persons with diabetes, Charles noted that 22% did not tolerate niacin, a percentage that he suggested could be reduced by lower-dose treatment (1,000–2,000 mg daily) in combination with statins. Overall, he stated, HbA_{1c} levels improved. Niacin was effective in reducing SD-LDL concentrations by 43% and in increasing HDL cholesterol by 36% (10). In a related open-label analysis of diabetic patients in his clinic, niacin (mean dose 2.8 g daily) in combination with atorvastatin (80 mg daily) reduced LDL cholesterol by 56% in 19 persons with diabetes, an effect greater than the 49% decrease seen in 22 persons receiving atorvastatin alone and the 20% decrease seen in 29 persons receiving niacin alone, with triglycerides decreasing by 69, 47, and 31%, respectively. HDL cholesterol increased by 42% with niacin, either given alone or in combination with atorvastatin, which itself did not increase the HDL cholesterol level (11). Charles noted that the CETP inhibitor torcetrapib may prove an important treatment, with studies showing that it doubles levels of HDL, with a 150% increase in HDL₂, an 80–100% decrease in SD-LDL, and anti-atherosclerotic effects in animals (12).

Triglyceride treatment

Angeliki Georgopoulos (Rochester, MN) reviewed triglyceride treatment guidelines, noting that the level recommended for treatment initiation decreased from 250 mg/dl in 1988, to 200 mg/dl in 1993, and to 150 mg/dl in 2001. Hypertriglyceridemia can cause chylomicron-related pancreatitis, the likelihood of which is decreased by lowering dietary fat and simple sugars with use of low-glycemic index foods, avoidance of alcohol, and avoidance of medications such as corticosteroids, β -blockers, and high-dose thiazides; by improving glycemia; and by using triglyceride-lowering drugs. Triglyceride lowering for CVD risk treatment is more complex. Triglycerides may be markers for atherogenic triglyceride-rich particles, including intermediate-density lipoproteins and remnant particles, which may directly lead to formation of foam cells, to atherosclerotic lesions, and

to unstable plaques. Triglycerides are also associated with other lipoprotein abnormalities, such as SD-LDL, low levels of HDL, and elevations in non-HDL cholesterol and apoB, and with hypercoagulability, endothelial dysfunction, decreased fibrinolysis, and a proinflammatory state (13).

Georgopoulos reviewed evidence that triglycerides are CVD risk markers from the World Health Organization study (14), showing that the presence of Q waves on the electrocardiogram is associated with elevations in triglycerides rather than cholesterol in multivariate analysis, the Paris Prospective Study (15) finding of increased risk at triglyceride levels >123 mg/dl, and evidence from the Framingham (16), PROCAM (Prospective Cardiovascular Munster) (17), and Copenhagen (18) studies of multivariate-adjusted doubling of risk for the upper tertiles at levels exceeding 118, 162, and 142 mg/dl, respectively. A meta-analysis has confirmed and extended these individual study findings (19). Furthermore, the Baltimore coronary observational long-term study showed significant difference in outcome comparing persons with fasting triglycerides above and below 100 mg/dl (20), so that this lower level might be an appropriate target for persons at increased risk.

There is evidence that CVD is associated with postprandial triglyceride elevation even after adjustment for fasting levels. Fifty-three percent of persons with triglycerides >260 mg/dl after a high-fat plus alcohol load had fasting triglyceride levels <150 mg/dl, although having hyperinsulinemia and decreased insulin sensitivity (21). In Georgopoulos's own studies using a non-alcohol-containing shake, only 8% of persons with postload triglycerides >200 mg/dl had fasting levels <100 mg/dl, although approximately half had levels <150 mg/dl, further suggesting the 100 mg/dl level as optimal (22). However, because of the difficulty of standardization of the triglyceride load, she suggested that routine measurement of postload triglycerides is not useful, with a ≥ 12 -h fasting level following ≥ 3 days alcohol abstinence probably offering optimal discrimination.

Certain genetic polymorphisms are associated with triglyceride elevations and increased CVD risk, showing interaction with environmental factors. Thus, persons with the apoE4 allele have particular risk with cigarette use, as do those

with the apoC-III promoter polymorphism who have the metabolic syndrome, those with the LPL polymorphism who are obese, and persons with polymorphisms of fatty acid binding protein 2 who have diabetes. In studies of fatty acid binding protein 2, the common Thr-54 polymorphism present in 40% of persons is associated with greater intestinal transport of fatty acids (23), leading to increased triglyceride levels, with Georgopoulos stating that association has been shown with stroke.

Briefly reviewing treatment, Georgopoulos noted that three fibrate trials, DIAS (Diabetes Atherosclerosis Intervention Study) (24), Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (25), and Helsinki (26) showed benefit of treatment with fenofibrate and gemfibrozil, although the Bezafibrate Infarction Prevention study failed to show benefit with bezafibrate treatment. Niacin treatment and fish oil supplementation were shown effective in the Coronary Drug Project (27) and GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) (28) studies. Furthermore, statins lower triglycerides to an extent similar to LDL cholesterol for persons with triglyceride levels >150 mg/dl, by decreasing production as well as by increasing LDL receptor-mediated clearance of remnants (29). Combination treatment with atorvastatin plus rosiglitazone may be particularly effective in reducing triglycerides, and there is evidence that simvastatin plus niacin both lowers triglycerides and reduces atherosclerosis (30). Lifestyle approaches, including exercise, cigarette discontinuation, weight loss, and fish intake also reduce triglycerides and CVD risk. Thus, although all these approaches to treatment also affect other lipoproteins and other CVD risk factors, there is suggestive evidence of benefit of triglyceride-targeted therapy.

In a study presented at the meeting, Altomonte et al. (abstract 926) studied the mechanism of action of fibrates, showing evidence that the nuclear Forkhead transcription factor Foxo1, suppression of which mediates aspects of insulin action, is also suppressed by fibrates in a high fructose-fed Syrian golden hamster model. Thus, under circumstances of resistance to the inhibitory effect of insulin on hepatic production of apoC-III and hence triglyceride-containing lipoproteins, fibrates may have insulin-

sensitizing effects, contributing to decreased apoC-III production and improved triglyceride metabolism in subjects with diabetic dyslipidemia. Dardik et al. (abstract 931) reported that administration of a dual peroxisome proliferator-activated receptor α/γ compound to obese Cynomolgus monkeys for 4 weeks led to a 59% decrease in triglycerides, a 51% increase in HDL cholesterol, a 37% decrease in fibrinogen, a 71% decrease in CRP, and a 21% decrease in food intake, with a 3% decrease in weight. In dogs, over 16 days triglycerides decreased 41% and weight decreased 5.4%, suggesting potential use in treatment of diabetes and insulin resistance-associated dyslipidemia. Hirano (abstract 938) reported the use of the angiotensin II receptor blocker olmesartan in insulin-resistant versus control rats, showing blood pressure lowering in both but improvement in insulin sensitivity, lowering of fasting glucose, and reduction in hepatic triglycerides levels only in the insulin-resistant animals, suggesting that blockade of angiotensin action may decrease triglyceride production independent of effects on blood pressure.

Drexel et al. (abstract 933) prospectively followed 756 persons with angiogram-proven coronary disease, 164 of whom had type 2 diabetes, showing the latter group to have association of a composite factor based on triglycerides, HDL, and apoA1 but not of a factor based on LDL cholesterol and apoB with vascular end points during a 2.3-year follow-up. Chu et al. (abstract 334) randomized 26 nondiabetic persons with insulin resistance and both triglycerides and cholesterol >200 mg/dl to 40 mg rosuvastatin daily vs. 600 mg gemfibrozil twice daily, for 3 months, showing a decrease in triglycerides from 255 to 143 vs. 292 to 150 mg/dl, an increase in HDL cholesterol from 41 to 45 vs. from 41 to 46 mg/dl, and a decrease in C-reactive protein (CRP) from 6.3 to 2.4 vs. 4.4 to 3.4 mg/l. LDL cholesterol decreased from 157 to 59 mg/dl with rosuvastatin versus no change with gemfibrozil, suggesting the former to be preferable. Betteridge and Gibson (abstract 927) compared the effects of rosuvastatin with atorvastatin in 509 patients with type 2 diabetes. Non-HDL cholesterol decreased 45 vs. 36% with 10-mg doses and 51 vs. 42% with 20-mg doses, respectively, from baseline levels of 166 mg/dl, while triglycerides decreased 22

vs. 17% and 23 vs. 20%, respectively, from baseline levels of 184 mg/dl.

Grundy et al. (abstract 29-LB) randomized 197 persons with diabetes, HDL cholesterol <40 mg/dl (men) or <50 (women), and triglycerides >150 mg/dl to 1,000–1,500 mg niacin plus 40 mg lovastatin versus 200 mg fenofibrate daily, showing a 32 vs. 3% fall in LDL cholesterol, a 23 vs. 6% fall in lipoprotein(a), and a 34 vs. 17% fall in non-HDL cholesterol. HDL increased 12% with fenofibrate, 14% with 1,000 mg niacin, and 26% with 1,500 mg niacin. Grundy et al. (abstracts 534 and 935) compared 18 weeks of treatment with 20 mg/day simvastatin plus 160 mg/day fenofibrate versus 20 mg/day simvastatin in 618 persons with fasting triglycerides between 150 and 500 mg/dl and LDL cholesterol >130 mg/dl, 105 of whom had type 2 diabetes and 437 with the metabolic syndrome based on satisfying three or more NCEP (National Cholesterol Education Program) ATP (Adult Treatment Panel) III criteria. In the overall group, triglycerides decreased 43 vs. 20%, LDL cholesterol decreased 31 vs. 26%, apoB decreased 33 vs. 23%, and HDL cholesterol increased 19 vs. 10%, with all differences significant and the diabetic and metabolic syndrome subgroups showing similar patterns of response. More persons converted to the less atherogenic pattern of buoyant LDL particles with the combination. No myopathy occurred in the 411 persons receiving the combination.

ApoB, a novel target

At a symposium on approaches to lipid-lowering treatment in persons with diabetes, Allan D. Sniderman (Montreal, Canada) presented a series of analyses of the effects of hypertriglyceridemia and elevated apoB, concluding that the true target for treatment in diabetes should be the apoB rather than LDL cholesterol. Each LDL and VLDL particle has one apoB molecule, and on average there are nine LDL particles for every circulating VLDL. Without measurement of apoB, Sniderman noted, one cannot distinguish persons with hypertriglyceridemia and large particles whose apoB is normal and who have normal VLDL secretion and those who have increased VLDL production and increased apoB levels with higher CVD risk (31). There is constitutive hepatic apoB production, with most apoB hydrolyzed after synthesis and salvage of

apoB associated with cholesterol ester. Subsequently triglycerides are added, and the VLDL particle is secreted. Increased hepatic fatty acid flux increases cholesterol ester formation, so that not only triglycerides but apoB cholesterol ester is increased, ultimately leading to greater production of SD-LDL particles.

Analyzing lipid phenotypes in insulin-treated persons with type 2 diabetes, ~20% have increased LDL, of whom approximately half have high triglyceride levels. If apoB is measured, however, 40% have increased levels. Similar results are obtained with nuclear magnetic resonance analysis of plasma lipids to assess SD-LDL particles. As the number of metabolic syndrome markers increases, the LDL cholesterol level does not change but apoB levels increase, suggesting an increase in the number of atherogenic particles. Levels of apoB correlate significantly with insulin sensitivity, fasting and 2-h glucose, blood pressure, fibrinogen, plasminogen activator inhibitor 1, and LDL size, whereas LDL levels per se are, Sniderman stated, “associated with almost nothing” (32). The ACCESS (Atorvastatin Comparative Cholesterol Efficacy and Safety Study), which studied 3,916 persons treated with atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin, showed that both LDL and non-HDL cholesterol decreased to near target levels with atorvastatin but that apoB levels did not fall to goal, so that the atherogenic particle number may not be decreased unless the LDL is reduced to ~50 mg/dl, suggesting that the LDL particle number is “the critical determinant” (33). Sniderman suggested that use of apoB measurement has a well-standardized assay and that, because fasting samples are not required, this allows a better approach to lipid treatment. In the 4S (Scandinavian Simvastatin Survival Study), for example, there is a clearer relationship of mortality reduction to the decrease in apoB than to that in LDL (34), so that adjustment of statin dosage to achieve apoB <85 mg/dl, about the 20th percentile of the population, would, Sniderman stated, allow more rational treatment.

In a study presented at the ADA meeting, Lewis et al. (abstract 231) reported that rosiglitazone decreases the number of triglyceride-rich lipoprotein particles (based on measurement of apoB pool size) without lowering the plasma triglyceride concentration. Tawakol and King (ab-

stract 620) reported that 23 persons, 9 of whom had diabetes, with HDL <35 mg/dl (mean 28 mg/dl), receiving 30 mg pioglitazone daily plus an intermediate-release niacin (500 mg) daily for 2 months showed an 82% increase in HDL, with triglycerides decreasing from 247 to 129 mg/dl, suggesting a potentially important approach to treatment of this condition. There was no significant decrease in LDL cholesterol. Yu et al. (abstract 951) studied 72 statin-treated persons with type 2 diabetes receiving rosiglitazone 0, 4, or 8 mg daily for 12 weeks. LDL cholesterol showed no change versus a 7 and 10% increase, but with increase in LDL particle buoyancy and LDL cholesterol-to-LDL apoB ratios, suggesting reduction in SD-LDL.

Metabolic syndrome

The DPP (Diabetes Prevention Program) Research Group (Rockville, MD) (abstract 982) compared persons in the placebo group who continued to have impaired glucose tolerance with those who progressed to diabetes, showing little change in systolic blood pressure, triglycerides, HDL or non-HDL cholesterol, or LDL size, suggesting that the cardiovascular risk factor profile typical of early type 2 diabetes is not very different from that of impaired glucose tolerance and implying that it is the insulin-resistant phenotype that is largely responsible for the dyslipidemia characteristic of states of dysglycemia. At a symposium on the metabolic syndrome, Jean-Pierre Després discussed the contribution of abnormal fat distribution to the syndrome, stating that although insulin resistance is the core element, from a clinical standpoint, the most important aspect is the abdominal obesity phenotype. "We have engineered [an] environment where we burn less and less calories," he stated, "combined with [a] toxic diet . . . The disease that you're dealing with, type 2 diabetes, is now seen in teenagers." Overweight and obesity may be defined based on BMI, with increased risk at 25–29.9 kg/m², high risk at 30–34.9 kg/m², very high risk at 35–39.9 kg/m², and extremely high risk at ≥40 kg/m², but there is heterogeneity in risk for a given BMI, as pointed out originally by Jean Vague, who in 1947 first used the terms android and gynoid obesity to describe persons with and without increased abdominal girth (35). Per Bjorntorp showed that the 13.5-year inci-

dence of type 2 diabetes is associated with abdominal girth and with BMI (36). The use of imaging to distinguish subcutaneous from visceral adipose tissue has called attention to the importance of the latter, although Després noted that total fat mass is strongly correlated with visceral fat, so that it is important to compare persons with similar total fat and differences in visceral adipose tissue to assess the contribution of the latter to insulin resistance, elevated triglycerides, low HDL cholesterol, increased apoB, SD-LDL, inflammatory profile, glucose intolerance, impaired fibrinolysis, hypertension, and endothelial dysfunction. Using gel electrophoresis to separate LDL based on particle size and quantity, the Quebec Cardiovascular Study showed that persons with peak LDL particle diameter <256.4 Å as well as apoB>120 mg/dl have a marked increase in CVD risk (37), with follow-up of the study showing worsening of event-free survival as LDL size tertile goes from larger to smaller. LDL particle size shows no correlation with the LDL cholesterol, but it is strongly correlated with triglyceride and HDL cholesterol concentrations and with the cholesterol-to-HDL cholesterol ratio.

Ridker has shown the additive risk of abnormality in both traditional lipid measures and CRP (38), with the latter "very sensitive to an expanding visceral depot," with waist circumference strongly predictive of CRP level. Després suggested that visceral fat "is a remarkable endocrine organ which will release inflammatory cytokines," with both tumor necrosis factor (TNF)- α and interleukin (IL)-6 predicting CRP levels. Adiponectin has antiatherogenic and antidiabetogenic properties, and there is an independent association of visceral adipose mass and adiponectin with HDL cholesterol, with higher adiponectin at any visceral fat level predicting higher HDL and lower CVD event rates. Increased visceral adipose tissue leads to increased hepatic triglyceride production and higher free fatty acid (FFA) levels. Després suggested that, alternatively, visceral adiposity may be viewed as a marker of reduced ability to store excess energy in subcutaneous adipose tissue, with a large insulin-sensitive adipose tissue mass cardioprotective from a metabolic viewpoint. Thiazolidinediones may increase the capacity of this tissue to store fat, whereas once the visceral adiposity phenotype is established, there

may be an ongoing pattern of insulin resistance. He noted that the ATP-III criteria should not be thought of as a definition of the metabolic syndrome but rather as a set of criteria to be used in identifying these persons. Thus, the metabolic syndrome is in certain ways as strong a risk factor for CVD as diabetes, further pointing out the importance of abdominal obesity (39), with the combination of fasting hyperinsulinemia, increased apoB, and SD-LDL associated with a 20-fold increase in CVD risk (40). In a report at the ADA meeting, Blackburn et al. (abstract 232), from Després's group, reported that women with coronary artery disease had higher triglyceride levels, lower HDL cholesterol concentrations, and smaller LDL particles than control subjects without coronary disease, suggesting that in addition to LDL cholesterol, the size of LDL particles should be assessed in evaluation of coronary disease risk in women.

John S. Yudkin (London, U.K.) discussed the interrelationship of inflammation and the metabolic syndrome, noting that low-grade inflammation is associated with insulin resistance and endothelial dysfunction and that adipose tissue generates inflammatory cytokines that may link insulin resistance with vascular disease. Comparing persons in the highest quartile of insulin levels with those having lower fasting insulin, dyslipidemia, procoagulant changes, inflammation, hypertension, and endothelial dysfunction are seen. Comparing the top quartile of BMI, however, one can equally explain the clustering of endothelial dysfunction with the above abnormal findings, suggesting excess body fat to be the underlying explanation. Yudkin referred to his 1999 proposal that the origin of the inflammatory state and of endothelial dysfunction was adipocyte-generated inflammatory cytokines (41), which correlate strongly with insulin resistance. He asked, "How does the liver, . . . skeletal muscle, . . . [and] the endothelium know that you are fat?" Circulating signal molecules from fat could include FFAs, adiponectin, IL-6 (particularly at the liver, where IL-6 increases CRP production), resistin, leptin, and TNF- α , although Yudkin noted that the latter cytokine does not exist in the circulation in sufficient quantities to achieve adequate free levels for action, given the presence of a circulating binding protein. Comparison of fasting arterial and venous IL-6 and TNF- α suggests that

an explanatory factor may be ectopic fat (42), as also suggested by the association of nonalcoholic fatty liver disease and intramyocellular with liver and muscle insulin resistance, respectively, with local cytokine mechanisms offering another explanation, as nonalcoholic fatty liver disease is associated with increased hepatic TNF- α production.

Yudkin speculated that perivascular adipose tissue having characteristics of visceral fat may be of importance in the process. Under circumstances of high nutritive flow, there is increased shunt vessel opening, with insulin acting at very low concentrations to divert blood over periods of several minutes from nonnutritive to nutritive blood flow. Other mediators include serotonin, which induces vasoconstriction of the nutritive circuit. Non-nutritive circuit shunting enhances LPL action to increase triglyceride deposition. Using arteriolar cannulation of rat cremaster muscle to directly study effects of vasoactive substances, insulin has little effect in the physiological range, but with blockade of the metabolic component of insulin signaling it produces vasoconstriction, whereas blockade of the anabolic component of insulin action leads to vasodilatation. Yudkin suggested the dual effect to be NO dependent via the metabolic pathway and to involve endothelin-1 via the anabolic pathway, with both effects normally balanced. In an obese rodent model, the vasoconstrictive response predominates and NO synthase expression is low. Morphologic analysis shows increased levels of perivascular fat in the obese animals, leading Yudkin to suggest the hypothesis that vascular insulin resistance is due to a "vasocrine" action of perivascular fat, perhaps caused by secretion of TNF- α (possibly entering the local arteriolar circulation at high levels because of increased endothelial permeability), IL-6, and FFAs, which inhibit the NO pathway leading to unbalanced endothelin-1, contributing to insulin resistance. Similarly, Yudkin speculated, epicardial fat may cause particularly prominent coronary vasoconstrictive effects, and at the level of the kidney, fatty tissue may cause microalbuminuria.

Aldons J. Lusis (Los Angeles, CA) discussed genetic approaches to the metabolic syndrome and atherosclerosis, addressing human studies, mouse studies, and a combination of genetics and genomic analyses. Attributing both atherosclerosis and the

metabolic syndrome to a very large gene network that can be perturbed by both genetic and environmental factors, with current understanding only in barest outline, he described a set of familial combined hyperlipidemia studies, characterized by increased cholesterol and triglycerides, with dominant-like pattern of inheritance explaining ~20% of early heart disease. Familial combined hyperlipidemia overlaps with certain aspects of the metabolic syndrome. These individuals overproduce triglyceride-rich VLDL, giving rise to SD-LDL. Aspects of the genes involved in this have been identified with genome scans of Dutch and Finnish populations, which suggest an abnormality of chromosome 1q (also involved in type 2 diabetes), showing association with upstream transcription factor 1 (43). This transcription factor recognizes a CACGTG nucleotide motif termed "E box." It regulates several genes involved in lipid and glucose metabolism and is responsive to dietary carbohydrate. Upstream transcription factor 1 stimulates fatty acid synthase, potentially explaining the association with increased VLDL levels, and has effects on inflammatory genes, including cyclooxygenase, and on glucose metabolism genes. Animal studies may also be used to determine genetic abnormalities of the metabolic syndrome and atherosclerosis. A locus on chromosome 6 segregates with both atherosclerosis and hyperinsulinemia, with evidence of both protective and atherosclerosis-producing genes. 5-lipoxygenase exists in this locus, oxidizing arachidonic acid to produce leukotrienes, expressed in leukocytes, with animals not expressing this gene protected against atherosclerosis. In human studies, homozygosity of the DD allele is associated with increased carotid IMT and with elevations in CRP and IL-6 (44), suggesting that leukotriene inhibitors might be of therapeutic benefit in CVD prevention. Lusis reviewed the use of a network concept to understand the causal interaction of multiple genes in animal models using microarray expression analysis to identify potential effects of genes. Using a genetic cross of DBA and B6 mice, thousands of genes have differential expression, with clustering of different gene sets. There are ~12 different loci contributing to body fat or to visceral fat, for example, allowing determination of a number of candidate genes that may underlie the trait of interest. Thus, rather than assessing a single perturbation with a "knockout" or overexpression, it is possible to assess interactions

of multiple genes with common phenotypic findings. As the *db* mouse with mutation in the leptin receptor derives from these two strains, this approach to analysis may allow understanding of the molecular factors underlying the development of diabetes in this model.

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