

# Approaches to Cardiovascular Disease and Its Treatment

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This is the third of a series of articles reviewing presentations at the 63rd annual scientific session of the American Diabetes Association (ADA), held in New Orleans, Louisiana, June 2003.

## Cardiovascular disease

Barbara Howard (Hyattsville, MD) gave the Kelley West lecture, in which she discussed the Strong Heart Study and the relationship between diabetes and cardiovascular disease (CVD). The study, which began in 1988 in three American Indian communities, describes "the epidemic of CVD and diabetes among this population." A total of 4,549 individuals age 45–74 years of age living in the Hela River Indian reservation in Arizona, including Pima, Sioux, and Dakota Indians, were studied with examinations at 5-year intervals and ongoing yearly surveillance of CVD mortality and events. Comparing the study population with their counterparts in the general populations of North and South Dakota, Arizona, and Oklahoma, levels of total and CVD mortality are ~2-fold higher among women and 1.5-fold higher among men. Similarly, carotid ultrasound studies show increased atherosclerosis among Indian men and women compared with other populations. There also appear to be trends to increasing CVD rates over the decade of the study.

Diabetes is very prevalent among American Indian communities. In the Strong Heart Study, rates exceed 60% in Arizona and 40% in the Oklahoma and Dakota groups. At 8-year follow-up, CVD rates are markedly increased among people with diabetes; coronary heart disease

(CHD) risks are eight- and threefold higher among women and men with diabetes, respectively. If, as Howard suggested, CVD takes 15–20 years to develop, one would expect a lag time of approximately this duration between the development of diabetes and that of CVD. This appears to be the case in the studied population, suggesting that the current epidemic of diabetes in the U.S. population will result in an increase in CVD rates, reversing current trends to improvement.

Comparing the relative strength of risk factors in individuals with and without diabetes, age has a similar effect, gender is less important, and the additional risk conveyed by blood pressure and, particularly, lipids is considerably greater among individuals with diabetes. One implication is that equations to calculate risk must be developed separately for individuals with and without diabetes. Even after adjusting for risk factors, there is increased CVD risk among people with diabetes.

The relationship between albuminuria and CVD was found to be extremely high, as in other populations. "It's not just the fact that people with renal disease have high blood pressure," as echocardiographic data suggest marked worsening in ventricular function among individuals with albuminuria, which may indicate a generalized microvascular abnormality rather than simply the presence of incipient renal disease. This is a population with marked insulin resistance. Both the Adult Treatment Panel III definition of metabolic syndrome and the homeostasis model assessment of insulin resistance index were strong predictors of diabetes,

but they did not appear to be strong CVD risk predictors among people without diabetes. Howard interpreted this finding to imply that the high rates of both insulin resistance and diabetes in this population lead to the development of diabetes before that of CVD, so that insulin resistance loses significance in multivariate analysis. Genetic studies are also being carried out in families in this group. The characterization of >30 family members per family in >100 families gives the potential to understand the degree of heritability of specific CVD characteristics and risk factors with stratification by diabetes status. Many insulin resistance-related characteristics, Howard noted, predict both diabetes and CVD.

Inflammation is part of the atherosclerotic process. Fibrinogen reflects inflammation, thrombosis, and perhaps other disorders and is a strong CVD predictor that also correlates with echocardiographic abnormalities. C-reactive protein (CRP) levels are very high in the studied population. Intermediate but not marked degrees of increase in CRP are associated with increased CVD, while higher CRP levels appear to reflect a high level of "pathogen burden" in this population rather than being markers of atherosclerosis-related inflammation. Adipose tissue plays a key role in insulin resistance, is associated with inflammation, and may be important in the genesis of CVD.

Diabetes was associated with a number of echocardiographic abnormalities in the Strong Heart Study, including abnormal diastolic filling and left ventricular (LV) hypertrophy. LV hypertrophy, low ejection fraction, and the E-A ratio, a measure of diastolic filling, are predictors of CVD death. The resting electrocardiogram (ECG) also was found of important prognostic significance, with ST depression of the sort usually regarded as "non-specific" and lengthening of the QT interval having strong predictive power for CVD and total mortality. To summarize, Howard stated, the "rising tide of CVD and diabetes . . . is going to happen in other populations and increasingly contribute to CVD in the U.S.," with lip-

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**Abbreviations:** CAC, coronary artery calcification; CAD, coronary artery disease; CAN, cardiac autonomic neuropathy; CRP, C-reactive protein; CVD, cardiovascular disease; EBCT, electron beam computerized tomography; ECG, electrocardiogram; HRV, heart rate variability; IMT, intima-medial wall thickness; LV, left ventricular; NAFLD, nonalcoholic fatty liver disease; NCEP, National Cholesterol Education Program.

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ids, blood pressure, fibrinogen, and inflammation related to atherosclerosis and insulin resistance.

### Cardiac testing in diabetes

John Rutherford (Dallas, TX) discussed who should be tested and with what tests, pointing out that, particularly among women, there has been improvement in individuals without diabetes versus worsening prognosis in people with diabetes over the past 2 decades. "Whatever the coronary syndrome you have," he noted, "the prognosis of a diabetic is almost twice as bad as [that of] a nondiabetic [patient]." People with diabetes have smaller diameter vessels on angiography, suggesting nonangiographically identifiable disease. Survival after an acute coronary syndrome is determined by age, presence of diabetes, and ventricular dysfunction, the latter more important in conveying prognosis than ST change and the tolerated duration of exercise. Age plays a crucial role, with survivors of myocardial infarction <50 years of age having 5% 5-year mortality, as compared with 13% for those age 60–70 years. Another risk factor is proteinuria, which Rutherford termed "a marker of vascular integrity."

He suggested that cardiac testing be performed on individuals with diabetes with any symptoms, typical or atypical; with abnormal ECG; with other evidence of vascular disease; on initiating an exercise program over age 35; or with two or more risk factors other than diabetes. In a study of 255 consecutive patients referred for stress testing using a simple clinical score, one point each for male sex, history of myocardial infarction, angina, diabetes, insulin use, and for each decade after age 40, an abnormal ECG doubled the risk of a positive test. Rutherford described a study in ~2,500 people comparing ECG treadmill exercise test with perfusion scanning, using the Duke treadmill score based on duration of exercise, degree of ST change, and development of angina. At 18 months, the mortality plus myocardial infarction rates for individuals with normal, mild, or severely abnormal perfusion scan were 0.3, 4.7, and 10%, respectively, while with low- and high-risk Duke treadmill score, the 18-month event rate was 0.9 vs. 7.7%. In individuals with diabetes undergoing imaging scans, a normal scan was associated with a 6% event rate over a 3-year follow-up, while a positive scan was associated

with a 27% event rate, with greater perfusion defect size increasing the event rate. In a 2.5-year follow-up of 4,000 nondiabetic and 1,000 diabetic individuals, for any level of abnormality on perfusion scan, the risk of adverse outcome, either death or myocardial infarction, is twice as great among people with diabetes. Fixed as well as reversible defects are associated with adverse outcome. Among individuals with abnormal adenosine single-photon emission computed tomography (SPECT) scanning, the rate of adverse outcome is worse in people with diabetes, particularly among women. Rutherford concluded that diabetes is a major prognostic marker, clinical criteria incompletely stratify patients, ECG stress testing is not as useful as perfusion scanning, and fixed as well as reversible defects on perfusion scanning offer prognostic information.

In further discussion of this topic, John Dent (Charlottesville, VA) discussed noninvasive stress testing. Acute clinical syndromes are caused by plaque rupture and thrombosis, and patients who have had such an episode need thorough evaluation. Over the past decade, Dent stated that cardiologists have realized that "diabetic patients are basically coronary patients with high sugars," referring to the Finnish study (Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998) showing that individuals with diabetes "are practically equivalent to the patient with known coronary artery disease." Stress tests are performed in stable patients using exercise with bicycle or treadmill or using dobutamine or a vasodilator, such as adenosine, to increase heart rate and contractility, with cardiac assessment using nuclear imaging, echocardiography, and/or the ECG. A stress test gives a probable diagnosis, and rather than simply informing us whether a person is normal or abnormal, it gives information pertaining to the extent and prognosis of coronary artery disease (CAD) in a given person. Understanding the concept of pretest likelihood is important. Based on a patient's symptoms, the greatest yield of stress testing is among people with "middling likelihood," where a positive test increases posttest likelihood to ~90%.

For the average person, ECG treadmill stress testing has 68% sensitivity and 77% specificity, although the test may be limited if a person is unable to exercise or has abnormal baseline ECG. Individuals with diabetes have testing sensitivity 50–60% and specificity 75–80%, so that the test remains useful. Dent noted that there is prognostic importance of the duration of a person's exercise, with >10 vs. <5 min exercise associated with 80 vs. 50% 14-year survival, and that "inability to have a treadmill is probably [associated with] even a higher mortality."

Stress echocardiography, performed before and within 1 min after exercise, studies abnormality of global LV systolic function and local wall changes, and has 70–80% sensitivity and 85% specificity for diagnosis of coronary disease. Among people with diabetes, a history of myocardial infarction and the number of abnormal wall segments are additive in predicting event likelihood, suggesting value over that of ECG testing, with the finding of multiple abnormal segments suggesting potential benefit from intervention. The test requires precise attention to technique, as in some individuals visualization is inadequate, or false-positive results are found, or imaging is performed too late, producing false-negatives.

Technetium-sestamibi, used for nuclear imaging of local coronary artery blood flow and estimation of global LV function, has 85–90% sensitivity, although specificity may be lower than that of stress echocardiography because of false-positive images caused by motion artifact, abdominal obesity, or breast tissue in women. Thallium is a weaker radiation emitter and is therefore no longer used by many laboratories, although it gives additional information pertaining to lung uptake. Positron emission tomography scanning measures myocardial viability, giving information about blood flow and glucose uptake; therefore, it should be used less for detection of disease than for establishing whether a patient would benefit from revascularization. Dent suggested that the choice of a testing modality "should be determined by local imaging expertise."

Trevor Orchard (Pittsburgh, PA) discussed electron beam computerized tomography (EBCT) measurement of coronary artery calcification (CAC) and carotid artery intima-medial wall thick-

ness (IMT) measurement, with the theme that “constant surveillance of heart disease [is needed] in all patients with diabetes.” In the Multiple Risk Factor Intervention Trial (MRFIT), 5,163 diabetic and 347,978 nondiabetic men were followed for an average of 12 years. CVD risk factors accounted for 68% of the excess CVD in individuals with diabetes, suggesting a role of risk factor modification (1). Similarly, in the U.K. Prospective Diabetes Study, LDL cholesterol, HDL, blood pressure, HbA<sub>1c</sub>, and cigarette smoking are highly predictive (2). The risk of CHD is ~10-fold greater in people with type 1 diabetes than in people without diabetes and shows a strong relationship to the presence of proteinuria.

EBCT has reasonable performance in a general population with 92–95% and 51–65% sensitivity and specificity for obstructive coronary disease. The test may be useful in individuals with borderline CAD risk. In individuals with type 1 diabetes, the prevalence of CAC is particularly increased in women. In type 2 diabetes, CAC correlates with the degree of insulin resistance and risk factors and is associated with a 1.7-fold increase in adjusted risk for clinical CHD, suggesting that the test may be less useful than in type 1 diabetes.

In Orchard’s study of people with type 1 diabetes, leukocyte count, cigarette use, blood pressure, and lipids were the main risk factors, while HbA<sub>1c</sub> did not significantly contribute to CAC, although it was associated with lower extremity vascular disease, suggesting that risk factors may differ for different vascular beds. Orchard noted that only one-quarter of individuals in the study had adequate control of risk factors. He pointed out that EBCT “permits a very rapid screening,” and that there is high correlation between the score and the risk of coronary arterial lesions. Because “not all plaques are calcified,” however, it is possible that vulnerable plaques are being missed, as EBCT may be more likely to identify stable than vulnerable plaques. Renal disease also increases calcification and therefore may increase the CAC score. Finally, diabetes itself is associated with medial wall vascular calcification, potentially causing a false-positive increase in CAC scores.

Carotid ultrasonography is a well-established imaging modality for detecting plaque and stenosis, with IMT a continuous measure related to carotid

atherosclerosis that, after adjustment for age and sex, is a predictor of risk of future events. Carotid IMT is associated with CHD events, although Orchard noted that the coronary and carotid beds are different. In the Atherosclerosis Risk in Communities (ARIC) study, increased IMT was associated with 1.38- and 1.17-fold adjusted increases in CHD risk in women and men, respectively (3), which Orchard considered to be of “borderline” importance. In the Rotterdam study, common carotid IMT did not add to clinical risk factors in the prediction of myocardial infarction and stroke (4). The CLASS study of subjects who had had cardiac surgery treated with colestipol and niacin showed correlation between annual change in IMT and risk of events (5). Carotid IMT is related to LDL cholesterol levels, as shown by a recent study comparing atorvastatin with pravastatin in which an association was found between carotid IMT and the degree of lipid lowering (6).

Carotid IMT is increased in diabetes and is associated with insulin resistance, microvascular complications, age, and glycemia among individuals with type 1 diabetes. Not all studies of people with type 2 diabetes have shown glucose levels to be related to carotid IMT, although in the Insulin Resistance Atherosclerosis Study (IRAS), IMT was increased in diabetes and glucose levels independently predicted IMT (7). Estrogen treatment of postmenopausal women was associated with lower IMT in this study, and increased IMT was not associated with IGT (8). Positive family history of diabetes is associated with IMT. Among individuals with newly diagnosed diabetes, both fasting and postprandial lipids have been shown to be associated with carotid IMT risk factors. Carotid IMT levels are similar in individuals with diabetes to those in individuals with CAD but without diabetes, and, in people with diabetes, carotid IMT is associated with blood pressure in women and with nephropathy in men. No studies have looked among people with diabetes to see whether IMT can be used as a predictor of event risk, as noted by Orchard, and IMT is not increased in young people with type 1 diabetes. In the EDIC follow-up of the Diabetes Control and Complications Trial (DCCT), however, IMT was increased over levels in individuals without diabetes and was higher in those who had received conven-

tional treatment than among those receiving intensive treatment, “a memory effect of benefit from the DCCT treatment group.” (See discussion by Lachin below.) Orchard concluded that IMT and CAC show moderately strong association with risk factors, but that their incremental predictive power for CAD is not certain, and suggested that changes in these measures over time may be more useful than single measurements.

Dan Siegler (Dusseldorf, Germany) discussed autonomic nervous system dysfunction in diabetes, suggesting that this has been neglected as a component of diabetic cardiac disease but is associated with poor prognosis. CVD, he noted, is the major driver of prognosis in diabetes. Cardiomyopathy may occur. Cardiac autonomic neuropathy (CAN) is characterized by reduced heart rate variability (HRV). HRV decreases with age, heart rate elevation, hypertension, obesity, the components of the metabolic syndrome, cigarette smoking, and pregnancy. There is an association of decreased HRV with hyperglycemia, HbA<sub>1c</sub>, duration of diabetes, and other complications, particularly polyneuropathy. A recent meta-analysis showed that mortality rates are ~30 vs. 13% in patients with and without CAN in 15 studies reviewed (9). Surveys following individuals both with and without diabetes have indicated that those in the lowest quartile of CAN have increased mortality, suggesting that low HRV is not only relevant to individuals with diabetes. CAN is associated with increased risk of major cardiac events and, in particular, of sudden death. Several minutes before lethal arrhythmia, parasympathetic tone decreases, leading to decreased HRV. Another marker of CAN, QTc interval prolongation to >440 ms, is associated with increased CVD risk both in diabetic and nondiabetic populations and may explain increased arrhythmia risk (10). Other findings in subjects with CAN include resting tachycardia, orthostatic hypotension with systolic fall exceeding 30 mmHg, decreased circadian rhythm of heart rate and blood pressure, and exercise intolerance with diastolic dysfunction and reduced increase in heart rate and blood pressure. Intraoperative cardiac instability with sudden fall in heart rate and blood pressure may be additional features of CAN. One question has been whether reduced pain perception in coronary disease is caused by CAN. Rates of

painless myocardial infarction rates are increased in people with diabetes, perhaps because of increased threshold for pain perception.

Decreased HRV during rest, deep breathing, standing, and with Valsalva; analysis of coefficient of variation, standard deviation, and frequency domain measures during a 24-h Holter monitoring; and measurement of blood pressure change with standing and of baroreflex sensitivity are used in CAD diagnosis. The method of spectral analysis involves mathematical decomposition of HRV amplitude versus frequency to produce very low, low, and high frequency bands that are associated with sympathetic, combined, and parasympathetic function. Decreased very low and absent low and high frequency bands may be seen with CAN, and very low and low frequency bands are the most sensitive. With these approaches, approximately half of patients with diabetes have abnormal findings, usually with both abnormal standard tests and 24-h HRV. To directly quantitate cardiac sympathetic denervation, positron emission tomography scanning may be employed. Siegler suggested that both functional and structural abnormalities may be responsible for the abnormal norepinephrine reuptake with this approach.

### Treatment of the metabolic syndrome

In a case study session at the ADA meeting, George Blackburn (Boston, MA) and Daniel Bessesen (Denver CO) discussed the question, "Do we know enough to treat the metabolic syndrome?" Bessesen noted that the International Classification of Diseases, Ninth Revision (ICD-9) code 277 can be used for metabolic syndrome, but suggested that "to make 277 work you have to add the other codes" for blood pressure, dyslipidemia, and obesity; therefore, it is uncertain whether the code itself is of any use in obtaining reimbursement in the clinical setting. Despite this bureaucratic anomaly, for individuals with obesity, hypertension, dyslipidemia, and diabetes, metabolic syndrome may be "the [actual] disease." Certainly, appropriate application of lipid, hypertension, and diabetes treatment guidelines, as well as administration of aspirin and perhaps vitamins such as folic acid and vitamin E, is, Bessesen suggested, appropriate.

The presentation began with a review of the National Cholesterol Education

Program (NCEP) guidelines (11). Three of five criteria must be fulfilled. Obesity is defined by waist circumference, using a tape measure at the superior iliac crest, parallel to the floor, at the end of a quiet expiration. This is an important measure of visceral adiposity, although underutilized in the community. The weight circumference is most useful in individuals with intermediate levels of BMI  $<35$  kg/m<sup>2</sup>. Blackburn suggested that we also consider weight gain in adults as a metabolic syndrome risk factor. The second criterion is impaired fasting glucose, at levels  $\geq 110$  and  $<126$  mg/dl, or diabetes. Related measurements that may be useful are of postprandial glucose or HbA<sub>1c</sub>, which may be important as a baseline measure, or actual performance of a 2-h glucose tolerance test, which is the more sensitive measure for abnormality of glycemia. Fasting glucose may be "the least sensitive" in view of the  $\beta$ -cell's ability to adapt to insulin resistance. Lipid abnormalities are additional criteria: triglyceride  $\geq 150$  mg/dl as the third and HDL  $<40$  mmHg in men and  $<50$  mmHg in women as the fourth. These have emerged as important markers for insulin resistance. The insulin assay itself is technically difficult, and there is no widely accepted cutoff for hyperinsulinemia and no consensus that insulin or insulin-glucose levels are as good as direct testing of insulin sensitivity. The fifth and final criterion of the NCEP typology is blood pressure, which "has gradually come down over time" from  $<140/90$  mmHg to the NCEP guideline levels  $<130/85$  to the Joint National Committee (JNC) 7 normal  $<120/80$  (12), with some evidence of increased risk even at  $>115/75$ . Many other measurements may be useful, including that of the inflammatory marker CRP and of urine microalbumin, and these may further add to the assessment of a given person.

In modifying behavior, most physicians "feel frustrated," Bessesen noted, stating, "We don't believe that we can do it and we don't believe that [the patient] could do it." The NCEP guidelines suggest the need to interact with the patient to change their diet and exercise habits, although this is often difficult and does not fit well with the traditional paradigm of the physician instructing the patient who then follows recommendations. "We have to . . . get the patient to think about his health problems . . . We need to be

more of a consultant . . . [or] a coach . . . A good coach has to believe in his team!" The "stages of change" model originally developed for cigarette cessation divides individuals into the stages of being precontemplative, contemplative, planning, acting, in maintenance, and in relapse. The same model can be used in assessing a person with the metabolic syndrome and in providing motivation appropriate to that individual. For those who are precontemplative, the physician or other health care provider can propose help if and when it is wished. For those contemplating and planning change, the physician can offer advice on appropriate strategies. Similarly, advice and encouragement can be given in the action, maintenance, and relapse stages. Physicians should consider that there is "a call to action" in addressing these issues.

Dietary techniques may involve instruction by dietitians and commercial approaches such as those of Take Off Pounds Sensibly (TOPS) and Weight Watchers and/or meal replacements such as SlimFast and "Lean Cuisine," which were used in the Diabetes Prevention Program and may be less costly than traditional medical interventions. It is important to redefine success in weight loss. An obese person with a 5% weight loss, or "even not gaining weight," may actually be highly successful in improving their health status. The use of the weight loss drugs sibutramine and orlistat have been shown effective and may be important in certain individuals in helping attain dietary goals. Activity recommendations should be to exercise at least 30 min daily, most days of the week, perhaps recommending use of pedometers to measure the number of steps an individual takes daily, which gives patients direct feedback of their performance. Sedentary people take  $\sim 3,000$  steps daily, modest activity is around 6,000 steps daily, and levels of activity associated with weight loss involve 10–13,000 steps daily. Organized classes may be important for patients to offer a practical next step. (See [www.americaonthemove.com](http://www.americaonthemove.com) in the U.S. and the "First Step Program" at [www.uwo.ca/actage/new/first\\_step.htm](http://www.uwo.ca/actage/new/first_step.htm) in Canada) Group sessions to help patients with dietary and exercise compliance may be useful. The question of when a given person is not responding to lifestyle or pharmacologic treatment becomes important with greater degrees of obesity, particu-

larly with multiple cycles of weight loss and weight regain. Gastric restriction surgical treatment of obesity may be an option, and Blackburn pointed out that the operation has been recommended as effective by a National Institutes of Health consensus panel (13).

### **Nonglycemic goals for type 2 diabetes treatment**

At a symposium addressing nonglycemic goals for treatment of type 2 diabetes, Harold Lebovitz (New York, NY) discussed a variety of approaches. For control of hypertension, he noted the importance of ACE inhibitor treatment. He suggested, however, that much of the apparent anti-atherosclerotic effect of the ACE inhibitor ramipril in the Heart Outcomes Protection Evaluation (HOPE) study came from its blood pressure-lowering effect. The agent was given at night to participants in the study, possibly reducing its apparent effect when blood pressure was measured during the day in the main trial report; however, a HOPE substudy of 24-h ambulatory blood pressure monitoring reported that mean systolic and diastolic pressures decreased by 12 and 5 mmHg, respectively (14), supporting his interpretation. Both ACE inhibitors and angiotensin receptor blockers are effective in individuals with diabetes, with losartan reducing proteinuria by half and decreasing the development of nephropathy and congestive heart failure by approximately one-third in the RENAAL study of 1,513 people with type 2 diabetes and clinical nephropathy (15).

The goal of LDL cholesterol lowering has been agreed upon at 100 mg/dl. Lebovitz noted, however, that the Heart Protection Study “changes our whole thought” about approaches to initiation of statins. A total of 20,536 subjects age 40–80 years, who were at increased risk of CVD because of existing CVD, diabetes, or hypertension, showed similar decreases in rates of CHD, of stroke, and of need for revascularization by approximately one-quarter. Relative benefit was similar in the 5,963 subjects with diabetes and in those whose baseline LDL was <100, 100–130, or >130 mg/dl. For every 1,000 subjects with diabetes treated for 5 years, 70 events could be avoided—a highly acceptable “number needed to treat” of 14 (16).

“We now need to ask,” Lebovitz continued, “Should we be as worried about

the HDL?” In the Veteran’s Administration HDL Intervention Trial (VA-HIT), 2,531 men below age 75, with baseline HDL  $\leq$ 40, LDL  $\leq$ 140, and triglyceride  $\leq$ 300 were treated for 5.1 years with gemfibrozil or placebo. On average, HDL increased from 31.5 to 33.5 and triglyceride fell from 160 to 110 mg/dl, with a 24% decrease in relative risk of events both in men with and without diabetes, although the absolute decrease in risk was greater for people with diabetes because of their higher baseline level (17). Further analysis suggested that it was not the fall in triglyceride but rather the increase in HDL cholesterol that was predictive of benefit (18).

Using both lipid and blood pressure treatment, as well as administration of aspirin, Lebovitz asked, could we even “do better?” In the Steno2 trial, 160 subjects with type 2 diabetes and microalbuminuria were randomized to usual care by general practitioners or to a special clinic with aggressive treatment goals (19). In 1993 the blood pressure and total cholesterol targets were set at 140/85 and 190, and in 2000 these were lowered to 130/80 and 175, respectively. The HbA<sub>1c</sub> goal was 6.5%, and the intervention group patients were treated with aspirin when possible. Glycemic treatment used a sulfonamide, metformin, both, or one of the oral agents plus NPH insulin, and the HbA<sub>1c</sub> achieved was around 8 and 9% in the intervention and control groups, with fewer than 15% of the former group achieving the <6.5% goal, which Lebovitz suggested implies that “long term control of glycemia is incredibly difficult.” Blood pressure treatment with ACE inhibitors, angiotensin receptor blockers, or both (a combination that Lebovitz suggested not be used in general) was administered to most of the intervention group, but only to 15% of the control subjects, statins to 57 vs. 14%, and aspirin to 60 vs. 10%, with effective lowering of blood pressure and lipids in the intensively treated group. The result was a 53% decrease in clinical macrovascular events, a 61% decrease in nephropathy, and a 58% decrease in retinopathy. Lebovitz concluded, “We have very good evidence for trying to get tight control of the nonglycemic parameters,” pointing out further that “it is a lot easier to control blood pressure and lipids and take an aspirin” than to control blood glucose.

Phil Zeitler (Denver, CO) discussed

nonglycemic treatment approaches for type 2 diabetes in children (see previous *Perspectives on the News* article for additional information at the ADA meeting on this topic). He mentioned the increasing prevalence of this condition, pointing out that in most pediatric diabetes clinics ~2% of patients had type 2 diabetes several decades ago, while now these children comprise ~40% of the pediatric diabetes population. Furthermore, type 2 diabetes in children has been reported around the world, suggesting a growing problem. Most children with type 2 diabetes are from ethnic minorities. Girls outnumber boys by two- to threefold, and the mean age at onset is 13, correlating with the middle of puberty, a time of reduced insulin sensitivity. A total of 80% have a positive family history, all are overweight and most obese, and 60% have physical findings such as acanthosis nigricans, suggesting the presence of insulin resistance.

The cause of the increasing level of type 2 diabetes in children appears to not be a change in genetic makeup of the population, which would be unlikely to have occurred over such a short period, but rather the lifestyle changes associated with a tripling of rates of childhood obesity over the past 4 decades. Diets made up largely of “fast foods” and snacks, high in caloric density and inexpensive with ever-enlarging portion sizes, as well as cultural changes, including the notion that one should never feel even slightly hungry, and the promulgation of food advertisement serve to further encourage weight increase. Furthermore, “our total caloric expenditure is falling,” with more automobile use and less walking, less active time in school, less play time at home, and more time spent in sedentary activities such as video games and computers, as well as television watching, which Zeitler noted has become irresistible to children because of the increasing number of television channels. There is lack of supervision, and participation in sports has become expensive, with a pernicious emphasis on excellence in physical activity so that if a child is not a “good athlete” he is encouraged to “get off the team.”

Zeitler expressed his belief that type 2 diabetes in children “must reflect a worse lifestyle abnormality than is generally present among the average [diabetic] adult.” Most belong to “type 2 families,” with 45% having a diabetic mother, 45%

a diabetic father, and 27% having both parents diabetic. Often the degree of glycemic control is poor in the parents of these children, with one study showing a mean HbA<sub>1c</sub> of 13%. Typically, family members are obese, diets are high in fat and low in fiber, and binge eating is prevalent. These children, usually watch television 3–5 h daily, reflecting their lack of physical activity.

In pathogenesis, Zeitler noted, “the disease is the same” as type 2 diabetes in adults, with decreases in both insulin action and insulin secretion. Type 2 diabetes in children is, however, frequently associated with nonglycemic problems, including hypertension, dyslipidemia, sleep apnea, nonalcoholic fatty liver disease (NAFLD), the polycystic ovarian syndrome, and, alarmingly, psychiatric illness, with many of these children receiving psychiatric drugs, frequently the newer atypical antipsychotic agents, which are potential causes of obesity. [These drugs have recently been recognized in a Food and Drug Administration advisory as risk factors for diabetes (20).] Because of the frequencies of sleep apnea and NAFLD, one must be alert for these conditions and treatment may be required. Sleep apnea may be more common than in adults with comparable degrees of obesity because of the common presence of pharyngeal lymphoid hyperplasia. NAFLD may be present in more than one-third of adolescents with type 2 diabetes, and perhaps in as many as half, with evidence of potential response to metformin.

A recent consensus statement of the American Heart Association and American Academy of Pediatrics recommended targets for glycemia, lipids, blood pressure, and weight (21). Behavior and diet interventions are safe and effective. The goal of LDL lowering was set at 160 mg/dl, although Zeitler pointed out that one might argue for levels <130 or <100 mg/dl. The goal of triglyceride was <150 mg/dl, with pharmacologic treatment recommended for levels >400 mg/dl, and the HDL goal was given as >35 mg/dl, although without therapeutic guidelines. The blood pressure goal is <95th percentile for age and body size, with consideration of pharmacologic treatment if no decrease with diet and exercise, and the weight goal is <95th percentile for age.

There are a number of important differences in approaches needed for

treatment of adults versus adolescents with diabetes. The latter typically have more severe lifestyle abnormalities, the additional insulin resistance of puberty, and the psychological stresses of their stage of life, as well as living with families. Adolescents have a long life expectancy. Girls may become pregnant, with the potential of increased risk for their offspring of their disease. In treatment, one must try to address lifestyle, diet, fitness, and exercise capacity. One must address the readiness for change of the person because a durable intervention will only be effective if the patient and their family are ready. The diet target should be cessation of weight gain for children who are still growing, with recommendation of 5–7% weight loss for those who have stopped growing. One should endeavor to identify deleterious habits, including use of convenience foods, snacks, large sizes, and soft drinks, which Zeitler described as “liquid sugar.” An important factor for many adolescents is their lack of cooking experience and of access to fruits and vegetables. The recognition and prevention of binge eating is important, and in formulating a treatment approach, one should identify “the meaning that eating has in these families” and the association of eating with family stress, domestic violence, and other psychosocial issues. One should also identify patterns of “electronics,” for homework and leisure activities, with “computers better than television because you can’t eat at the same time.” These patients should be encouraged to exercise 20–30 min per day, 5–6 days per week. Moderate aerobic exercise is appropriate, particularly as the maximal oxygen consumption of these children is decreased in comparison to that of matched obese individuals without diabetes, so that initiation of exercise is physically more difficult for them. “They’re intimidated by all those kids around them who do know how to exercise.”

Zeitler concluded by pointing out the need to treat “traditional” diabetes targets and, in addition, to address barriers to lifestyle change among adolescents, including social pressures, family behavior, and psychiatric issues. Obese children, he suggested, are very isolated and tend to “hang out with their parents,” while at the same time “they’re

searching for independence” and are resistant to advice from the diabetes team. “The long duration of disease, risk of complications, and risk to the next generation require that significant long-term change be the goal.”

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