

American Diabetes Association 60th Scientific Sessions, 2000

Cardiovascular disease in diabetes

ZACHARY T. BLOOMGARDEN, MD

This is the fourth of seven reports on the American Diabetes Association (ADA) 60th Scientific Sessions held in San Antonio, TX, in June 2000. It covers topics related to cardiovascular disease (CVD) in diabetes.

CVD Symposium

At a symposium held in conjunction with the meeting, Richard Nesto, Boston, MA, discussed screening for coronary heart disease (CHD) in diabetes. He stressed the importance of early treatment of acute myocardial infarction (MI), noting the increased mortality in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial with delay in diagnosis (1) and the high prehospitalization mortality in the Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (FINMONICA) study (2), which suggest the need for screening. This is particularly suggested by recent evidence that intensive risk factor modification improves the prognosis of patients with diabetes and CVD. The patient with diabetes may have either typical or atypical cardiac symptoms. Other patients requiring screening are those with abnormal resting electrocardiogram and those with other evidence of atherosclerosis; peripheral arterial disease, for example, is associated with a fourfold increase in CHD risk. Patients with macroalbuminuria have markedly increased CHD risk as well.

Nesto pointed out that autonomic neuropathy is associated with decreased sur-

vival and a high CHD incidence and that this group may respond to treatment with β -blockers in view of their increased sympathetic tone. Cardiac autonomic neuropathy may also result in increased variability in sympathetic activity within the heart, as seen after MI, a potential cause of arrhythmia. Additional indications for CHD screening are the presence of two or more risk factors (dyslipidemia, hypertension, cigarette smoking, or positive family history) and the sedentary patient beginning a vigorous exercise program. The yield of noninvasive testing of patients identified in this fashion is between 10 and 20%.

Nesto described a recent study of 925 individuals with type 2 diabetes, of whom 112 had a positive exercise electrocardiogram test, with 59 of the 112 having a positive thallium perfusion study. In another study, 136 patients were screened with Holter, exercise, or thallium studies; 40 had abnormal findings. Of those 40, approximately one-third had >50% coronary narrowing at catheterization. It should be noted that exercise electrocardiogram and radionuclide studies are less accurate with hypertension, diabetic or autonomic cardiomyopathy, renal insufficiency, or microvascular disease, all of which can cause segmental abnormality.

A problem with screening is the uncertainty as to whether nonsurgical interventions are beneficial. "You've got to be careful when you do angioplasty," Nesto stated, because "these procedures have a high re-intervention rate and may carry the patient

further on the path to surgery." Rapid and severe restenosis is more common with diabetes; therefore, because "intervention begets intervention," Nesto commented that "when we start screening we need to know what to do."

The Asymptomatic Cardiac Ischemia Pilot (ACIP) study suggested that there was better outcome after revascularization than with medical treatment (3). Once the patient is found to have CHD, aggressive preventive treatment, anti-ischemia medication, identification of patients who would benefit from revascularization, and patient education to recognize potential symptoms and act on them immediately are needed. Other tests to identify patients at risk of CHD are ultrafast computerized tomography to measure coronary calcification and ultrasound assessment of carotid artery disease. Markers such as lipoprotein(a), fibrinogen, C-reactive protein, and homocysteine may add further to the identification of patients at increased risk.

Byron Hoogwerf, Cleveland, OH, discussed further aspects of assessment and treatment of patients with diabetes and CHD. Studies with intravascular ultrasound show that asymptomatic CAD affected 17, 37, 60, 71, and 85% of transplant donor hearts of presumably asymptomatic individuals who died of other causes during the 3rd, 4th, 5th, 6th, and 7th decades of life. Among individuals with diabetes, these frequencies will be considerably higher. Other ultrasound studies suggest that the conventional angiogram may not be a good predictor of the degree of CHD (4). There is often eccentric arterial narrowing, which may not be well detected by angiography. Furthermore, the concentrically narrowed lumen may be of lesser risk than one with eccentric narrowing because of the likelihood that the latter contains a lipid-rich plaque at risk of rupture. Indeed, many patients who have an angiogram and subsequently have MI have <50% narrowing of the artery that causes the infarction.

Thus, Hoogwerf recommended functional testing for symptomatic and high-risk asymptomatic patients. Pharmacological or exercise stress are used to differentiate

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.

Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HOT, Hypertension Optimal Therapy; IL, interleukin; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; PAI, plasminogen activator inhibitor; SHOW, Study of Health Outcomes Weight Loss; TNF, tumor necrosis factor; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

between reversible and fixed defects on thallium perfusion scans, which measure impaired flow of radionucleotide, or on echocardiography, which measures wall motion abnormality. If the functional test is positive, the current approach is to perform angiography. However, a negative angiogram should not lead to the message that there is no CHD, but rather should be used to explain to the patient the importance of medical treatment. Hoogerwerf stated that “stents are falling out of favor,” suggesting that reassessment of our overall approach to CHD in patients with diabetes will likely be important.

Diagnosis of CVD

Several studies reported at the ADA meeting assessed new diagnostic modalities. Gonzalez et al. (abstract 615) performed carotid ultrasound on 171 nondiabetic individuals followed on average for 3.2 years, with 17 developing diabetes. Their intima-medial thickness was 738 vs. 672 μm , suggesting that carotid atherosclerosis can antedate the development of diabetes, although statistical adjustment for other risk factors appeared to explain most of this finding. Watanabe et al. (abstract 617) performed nuclear magnetic resonance angiographic studies of the intracranial arteries and ultrasonographic studies of the abdominal aorta, cervical, and lower-extremity arteries in 119 diabetic and 113 age- and sex-matched nondiabetic patients who had undergone elective coronary artery bypass grafting surgery. Cervical and lower-extremity atherosclerosis were more common with diabetes, whereas intracranial and abdominal aortic atherosclerosis were not, with diabetic patients 1.8-fold more likely to have extracoronary disease than those without diabetes. Yamagami et al. (abstract 619) evaluated electron beam computed tomography coronary calcium scores in 101 patients with and 186 without diabetes who had had coronary angiography. Scores over 82 gave 68% sensitivity and 68% specificity, whereas a score exceeding 200 gave a 62% sensitivity and 98% specificity in diabetic patients. Higher HbA_{1c}, lower HDL cholesterol, and coronary calcium score—but not blood pressure, age, or total cholesterol—were predictors of angiographic coronary disease.

Bierman Lecture

John Colwell, Charleston, SC, gave the Bierman Lecture, entitled “Prevention of Cardiovascular Events in People With Diabetes.” At the first consensus conference on

this topic >10 years ago, it was recognized that the risk of CHD increases exponentially for diabetic patients, with risk factors further increasing this. In the Multiple Risk Factor Intervention Trial (MRFIT), 12-year analysis of CHD death showed increased risk with diabetes, with further increase by hypertension, hypercholesterolemia, or cigarette use to a greater extent than in nondiabetic individuals (5). We now have evidence “to firmly guide the prevention of cardiovascular events in people with diabetes.” The results of the Diabetes Control and Complications Trial (DCCT) (6) and U.K. Prospective Diabetes Study (UKPDS) (7) show the importance of glycemic control, although “strong evidence for effect on macrovascular disease was not shown.” The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction Study shows evidence that glycemic control may decrease myocardial infarction in type 2 diabetes (8). However, the Veteran’s Administration Collaborative Study (VACS) actually showed a trend toward increased CHD with intensive treatment, “so we have conflicting evidence.”

“In striking contrast,” Colwell commented, “the results of modest blood pressure lowering” showed benefit for CHD as well as microvascular disease in the UKPDS (9). The Hypertension Optimal Therapy (HOT) trial similarly showed 51% risk reduction in the group with diabetes randomized to a goal diastolic blood pressure of 80 mmHg as compared with 90 mmHg (10). The Systolic Hypertension in Europe study showed an ~60% decrease in risk with lowering of systolic blood pressure (11). Statin treatment of patients with diabetes was shown to be beneficial in the Scandinavian Simvastatin Survival Study (4S) (12) and Cholesterol and Recurrent Events trial (13). Aspirin treatment lowers cardiovascular risk in patients with diabetes, with the Early Treatment Diabetic Retinopathy Study showing safety in retinopathy (14) and the HOT trial showing aspirin to give an additional 15% decrease in risk over blood pressure treatment without additional adverse effects. ACE inhibitors decreased the risk of a variety of cardiovascular end points by 20–37% in the 4.5-year Heart Outcomes Prevention Evaluation study (15). Finally, metformin treatment in the UKPDS significantly decreased MI- and diabetes-related mortality in overweight individuals with diabetes (16). Thus, a number of cardioprotective strategies can be used.

Colwell outlined important advances in knowledge of the pathogenesis of atherosclerosis. Early endothelial injury, with release of thromboxane by activated platelets, lipoprotein-macrophage interactions, and glycation are increased in diabetes and may respond to intensive insulin treatment. The late stages of atherosclerosis include plaque rupture, platelet adherence, and clot formation, all increased in diabetes by an underlying prothrombotic state caused by changes in the intrinsic coagulation system, increased platelet activity, and decreased thrombolytic activity. Platelets from both type 1 and type 2 diabetic patients show increased thromboxane release, and plasminogen activator inhibitor (PAI)-1 increases with insulin resistance as well as with diabetes. Most PAI-1 is present in platelets, and this may be the key regulatory protein in the fibrinolytic system. Increased PAI-1 is associated with increased thrombosis and is a predictor of CVD in humans. Levels may be lowered with weight loss, exercise, thiazolidinediones, metformin, and vitamin E in women. Aspirin may decrease platelet release of PAI-1. Glycation may decrease fibrinolysis and contribute further to the prothrombotic state. Thus, we need aggressive treatment of dyslipidemia, platelet dysfunction, and hypertension.

Whether there is a role for intensive glucose management requires ongoing clinical trials. CVD event rates and mortality among patients with diabetes are on the increase, although they are decreasing in individuals without diabetes (17). “The challenge now,” Colwell concluded, “is to translate this message of multifactorial risk factor reduction to our colleagues. Like a hurricane, atherosclerosis in people with diabetes starts slowly, chooses vulnerable areas to attack, and is widely destructive. In contrast to hurricanes, however, we now have the ability to prevent these trends in people with diabetes.”

Prevention of CVD

Markku Laakso, University of Kuopio, Finland, began a symposium on the prevention of CVD in diabetes, reviewing the interrelationships between diabetes and atherosclerosis. The risk of CVD increases in the prediabetic state. CHD mortality is similar in individuals with type 2 diabetes and in those without diabetes who have had MI, with nearly a 50% 7-year mortality in individuals with both type 2 diabetes and a history of MI. Laakso asked, “What are the changes in CVD risk factors in

patients with diabetes? Can we prevent CVD by normalizing these risk factors?" He added several points to Colwell's, noting that the CVD risk factors particularly associated with diabetes are blood pressure, hypertriglyceridemia, low HDL cholesterol, hyperinsulinemia, and obesity. In the MRFIT, the higher the serum cholesterol, the higher the risk of CVD, in nondiabetic subjects and in diabetic subjects, but at every cholesterol level, patients with diabetes had a two- to threefold increase in risk. Similarly, blood pressure and cigarette smoking are risk factors in patients both with and without diabetes. Those with diabetes, however, show greater CVD risk for every level of the risk factor. High levels of LDL cholesterol are present in 35–40% of patients with diabetes, about the same fraction have low HDL, half have hypertension, and 10–20% smoke cigarettes, so most patients have readily modifiable risk factors. Laakso noted that half of patients with diabetes are >60 years of age, but that trials have focussed on younger patients, so we do not have definite evidence in the older age-group.

John B. Buse, Durham, NC, discussed the planned Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. The question being addressed is the relative benefit of treating glycemia versus lowering blood pressure and changing lipid levels. The final protocol is under review, with planning for 4–7 years of follow-up of ~10,000 patients with type 2 diabetes at high risk for CVD—either with clinical disease, subclinical disease, or two or more risk factors—with glucose, lipid, and blood pressure interventions. The glycemic target will be $HbA_{1c} < 6.0\%$ ("action level," 6.0) vs. $< 7.5\%$ ("action level," 7.9). Patients will be excluded if they have a history of severe hypoglycemia or evidence of type 1 diabetes, are unwilling to perform home glucose monitoring or inject insulin, or have serum creatinine > 1.5 times or alanine aminotransferase > 2 times the upper limit of normal. The intensively treated group will have somewhat greater frequency of contact, both in the clinic and by telephone, with study health care providers. At telephone contacts, the intensive group will aim for preprandial glucose of 100 mg/dl and postprandial glucose of 140 mg/dl, with testing frequency of four to eight times per day, whereas the standard treatment group will perform only limited home glucose monitoring. The major outcome will be CVD events, with a number of secondary

outcomes, including microvascular disease, quality of life, and cost, also being followed.

Rena R. Wing of Brown University discussed a planned behavioral intervention, the Study of Health Outcomes Weight Loss (SHOW) trial, a multicenter randomized clinical trial to evaluate the health effects of interventions designed to promote weight loss in 6,000 individuals with type 2 diabetes. Over 50% of adults in the U.S. are overweight (BMI > 25) or obese (BMI > 30). Obesity increases morbidity by increasing the prevalences of dyslipidemia, hypertension, diabetes, and some forms of cancer; 80% of patients with diabetes are overweight, and obesity increased diabetes 11.2-fold in the Nurses' Health Study (18). Among individuals with diabetes, two-thirds of those with BMI > 30 are currently trying to lose weight. Consumers in the U.S. spend \$33 billion annually in efforts to lose weight. Many studies show short-term benefits of weight loss in improving blood pressure, lipids, and glycemic control. The degree of weight loss over a 1-year period correlates with the degree of improvement in HbA_{1c} , lipids, and blood pressure.

There are, however, no long-term data on the effects of weight loss on CVD risk factors or on mortality. Indeed, epidemiological studies suggest that cycles of weight loss followed by weight gain may increase mortality, raising the concern that efforts at weight loss may ultimately be harmful. Wing discussed a 2-year study showing that a group with 5–10% weight loss had an initial improvement in lipids, followed by return to baseline by the end of the study period. The Swedish Obese Subjects (SOS) study with gastric surgery showed a dose-response between weight loss and CVD risk factors, including blood pressure, cholesterol, HDL, uric acid, and blood glucose at 2 years. Lipid benefit required a 30-kg weight loss in this very obese group, although lesser degrees of weight loss benefited the other risk factors (19). In the University Group Diabetes Program (UGDP) study, comparison of placebo with insulin treatment showed no change in mortality, perhaps in part because only the former group showed sustained weight loss. The Aberdeen Study of patients with diabetes showed an increase in life expectancy of 3.6 months per kilogram of weight loss in patients with diabetes who had lost weight (20). Men with diabetes who had a nutrition and exercise intervention showed an improvement in mortality in comparison with a nonrandomized control group (21). Finally, the World Health Organization

multinational study showed that weight loss was beneficial in individuals with BMI ≥ 30 but had a detrimental effect in those with BMI < 30 (22).

Some researchers have suggested that the benefits of weight loss are unproven (22). The SHOW trial is designed to address this question. Specific eligibility criteria, outcome measures, and intervention approaches are still being planned. Gastric surgery will not be included in the main study, but may be studied in a simultaneous trial. The decision as to whether to include pharmacological weight loss interventions in combination with the behavioral interventions has not been made. Hollander et al. (23) reported 6.2 vs. 4.3% weight loss with orlistat versus placebo in patients with diabetes at 1 year, and sibutramine has shown similar benefits, suggesting that such an approach is feasible.

Trevor J. Orchard of the University of Pittsburgh discussed the long-term follow-up of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a planned 10-year follow-up of 96% of the individuals originally enrolled in the DCCT. Participants with hypertension, dyslipidemia, and advanced complications were excluded from the DCCT, so one might not expect to have clinical differences in macrovascular outcome, and indeed none were found. Carotid intima-medial thickness measurements done after the conclusion of the DCCT showed no difference between women with diabetes and those in a nondiabetic control group and little difference between men with and without diabetes. There was no difference between the intensive treatment and control diabetic groups, and there was no relationship between HbA_{1c} and intima-medial thickness. The 4-year EDIC data similarly showed no association of glycemia with two indicators of macrovascular disease: intima-medial thickness and ankle-brachial index. In contrast, data on microvascular disease showed "strong continuing benefit of the DCCT intervention" on microalbuminuria, retinopathy, and neuropathy in the previous intensive therapy group.

Orchard pointed out, however, that "individuals who go on to intensive care may be more health conscious," so follow-up of a population of patients with type 1 diabetes based on glycemia may give a misleading picture. The intensive therapy regimen in the DCCT was associated with decreased dietary fat, lower LDL chole-

terol, and lower blood pressure, additional factors that might reduce CVD risk. In Orchard's Pittsburgh follow-up study of patients with type 1 diabetes, coronary disease was seen in 18% of patients after 35 years. CVD was strongly associated with age, duration of diabetes, and hypertension, but HbA_{1c} did not show an association. European studies also suggest little effect of glycemia on macrovascular disease. A family history of probable type 2 diabetes and the waist-to-hip ratio both correlated with CVD, suggesting that patients with features of both type 1 diabetes and type 2 diabetes may be particularly at risk. There is some evidence of adverse CVD effect of features of type 2 diabetes among patients with type 1 diabetes in the DCCT as well. Those in the top quintile of the intensive treatment group with the greatest weight gain had BMI of 31, in contrast to the top quintile of the conventional treatment group, with BMI of 27. This further suggests a subset of type 1 diabetic patients with features of type 2 diabetes, who may be at particular risk of heart disease. Similar analysis of the Pittsburgh study showed a greater frequency of hypertension among patients who gained weight with improved glycemic control.

Orchard concluded that intensive glycemic control is not strongly associated with CVD prevention and brought up the possibility of proatherosclerotic effects of insulin treatment. Further, he suggested that "glycemia may not always be bad in terms of atherosclerosis." High blood glucose might lead to more stable plaque formation and be less likely to cause coronary events, although potentially causing lower-extremity arterial insufficiency and contributing to the increased amputation rate in more hyperglycemic patients. An argument to the contrary made by Haffner, who chaired the session, is that stable ischemic coronary disease syndromes are not seen with increased frequency in these patients, as the hypothesis would seem to suggest.

CVD Abstracts

A number of studies at the ADA meeting addressed relevant aspects of CVD in diabetes. Olson and Orchard (abstract 740) reported on a 10-year follow-up of 658 patients with type 1 diabetes whose mean age was 28 years and diabetes duration was 19 years at baseline. Controlling for CVD risk factors, the finding of ischemia on electrocardiogram was associated with a 3.7-fold increase in mortality, and an ankle-brachial arterial pressure difference

≥ 75 mmHg was associated with a 2.8-fold increase in mortality. Hu et al. (abstract 81) reported that women with type 2 diabetes from the 121,518-person Nurses' Health Study had a 3.00-fold increase in relative risk of mortality, greater than the 2.48-fold increase in risk of women who had had an MI. The respective risks of fatal CHD were increased 6.04- and 6.65-fold. Individuals with both diabetes and past MI had 5.49-fold increased total and 14.0-fold increased CHD mortality. After <5 , 5–10, 10–15, 15–25, and >25 years of diabetes, total mortality risks were 1.69-, 2.03-, 2.56-, 3.07-, and 5.27-fold that of patients without diabetes, and CHD mortality increased 2.24-, 2.96-, 4.49-, 5.36-, and 13.3-fold. The excess risk of fatal CHD for women who had diabetes for ≥ 10 years was therefore similar to that conferred by a prior MI. Schellhase and Koepsell (abstract 777) reported that among 250 individuals with type 2 diabetes who had at least one microvascular complication, for each 1% increase in mean HbA_{1c}, there was a 26% increase in risk of a second complication, controlling for age, sex, and the presence of hypertension and hyperlipidemia. They comment that HbA_{1c} may be a marker for the underlying severity of disease rather than a direct mediator of complications, further suggesting the need for controlled studies.

Fish et al. (abstract 556) studied 200 patients undergoing coronary artery bypass graft surgery, 63 with known diabetes and 23 whose fasting glucose on day 3 was ≥ 126 mg/dl. Postoperative glucose >250 mg/dl increased the likelihood of readmission within 60 days or death 7.9-fold, whereas diagnosed diabetes increased this 3.8-fold. Postoperative glucose >250 mg/dl, but not diabetes per se, increased the length of stay from 6.5 to 10.6 days for the overall group, suggesting benefit of intensive treatment of postoperative hyperglycemia.

The atherosclerosis risk factor homocysteine shows important effects in diabetes. Emoto et al. (abstract 554) reported that plasma total homocysteine was associated with ultrasonographic intimal-medial thickness of the carotid and femoral arteries in 81 individuals with type 2 diabetes and 127 healthy control subjects. Hosoi et al. (abstract 219) reported that a common mutation in the enzyme methylenetetrahydrofolate reductase, which is involved in the folate-dependent remethylation of homocysteine to methionine, determining plasma homocysteine levels, was associated with an increased level of coronary

artery calcium by electron beam computed tomography, an indicator of underlying atherosclerotic disease. Mean scores among 238 patients with type 2 diabetes without evidence of CVD were 465 in homozygotes, 228 in heterozygotes, and 115 in patients without the mutation.

Another important factor is ACE gene polymorphism. Gao et al. (abstract 559) reported that 71% of 176 type 2 diabetic patients with and 38% of those without the D allele of the ACE gene insertion/deletion polymorphism showed ultrasound evidence of carotid atherosclerosis, with the DD genotype increasing the atherosclerosis risk 3.9-fold, controlling for age, sex, and hypertension. Seyoum et al. (abstract 601) reported that 6.8% of 205 and 321 individuals with type 2 diabetes having the DD and DI phenotype and 1.4% of the 140 patients with the II phenotype had MI in the Appropriate Blood Pressure Control in Diabetes trial.

Other evidence also suggests that insulin resistance is related to CVD in type 2 diabetes. Bonora et al. (abstract 83) reported a correlation between insulin resistance as estimated by homeostasis model assessment of 267 CVD events in 960 individuals with type 2 diabetes followed for a mean time of 52 months, with age, cigarette smoking, and HbA_{1c} as other significant predictors. Murase et al. (abstract 588) studied 20 nondiabetic Japanese men with familial hypercholesterolemia, having total cholesterol of 334 mg/dl. The degree of arteriographic coronary stenosis correlated with the fasting insulin level, but not with cholesterol, triglyceride, HDL, age, BMI, systolic blood pressure, or smoking, suggesting that hyperinsulinemia or insulin resistance may potentiate coronary atherosclerosis in patients with severe hypercholesterolemia.

Quinones et al. (abstract 598) reported that 9 insulin-sensitive Mexican-Americans had more than a twofold greater increase in positron emission tomography coronary blood flow in response to cold pressor testing than did 19 individuals with insulin resistance. The latter group had greater degree of obesity, higher blood pressure and triglyceride, and lower HDL cholesterol levels, suggesting many potential mediators. Takami et al. (abstract 608) reported that both intra-abdominal and abdominal subcutaneous fat, measured by computerized tomography, but not total body fat, were correlated with common carotid artery intima-medial thickness in a study of 707 Japanese men of mean age 50

years. Adjustment for glucose tolerance, insulin resistance, serum triglyceride, HDL cholesterol, and systolic blood pressure nullified the correlation of intima-medial thickness with abdominal fat, suggesting it to be mediated by factors causing insulin resistance. Finally, Coggins et al. (abstract 983) used contrast-enhanced ultrasound to assess capillary blood volume and flow velocity in the forearm with saline and insulin infusion in 11 normal-weight and 6 obese individuals. The test showed little change in blood flow with insulin in either group, but an increase in capillary volume in the obese group, suggesting resistance to capillary recruitment to be a feature of the insulin response in obese individuals.

Inflammatory mediators may be related to the development of type 2 diabetes and to the process of atherosclerosis. Mubarak et al. (abstract 353) treated 50 patients with diabetes and periodontal disease for 3 months, showing a decrease by >40% in oxygen free radical generation by polymorphonuclear cells and monocytes, with a fall in interleukin (IL)-1 β and prostaglandin E₂, suggesting a role of dental disease in the inflammatory state in patients with diabetes. Moore et al. (abstract 587) reported a significant association of missing teeth, the number of decayed or filled tooth surfaces, and oral candidal lesions with coronary disease among 406 patients with type 1 diabetes.

Ganda et al. (abstract 558) followed 95 patients with diabetes for 8 years, reporting mortality of 41 vs. 9% for patients with fibrinogen above or below the median value of 330 mg/dl. Fibrinogen remained significant after adjustment for age, while C-reactive protein, baseline CVD, hypertension, and obesity did not show significant contribution to mortality, suggesting that enhanced thrombogenesis increases the development of atherosclerosis in patients with both type 1 and 2 diabetes. Chaturvedi et al. (abstract 627) reported elevated plasma C-reactive protein levels to be associated with retinopathy, albuminuria, and cardiac or peripheral vascular disease among 536 patients with type 1 diabetes, at least partially explained by its association with HbA_{1c}, triglyceride, and obesity.

Kern et al. (abstract 96) studied the relationship between adipose tissue biopsy cytokine expression and insulin sensitivity in 41 individuals without diabetes with BMI between 19 and 63. Adipose tissue tumor necrosis factor (TNF) mRNA and, to a greater extent, TNF secretion increased with increasing obesity and with increasing

insulin resistance, although there was no change in plasma TNF. Expression of IL-6, a cytokine produced in part by adipocytes, also was highest in the most obese insulin-resistant individuals, and plasma IL-6 increased with increasing insulin resistance. Hanson and Pratley (abstract 1240) found IL-6 to be significantly associated with insulin resistance after adjusting for obesity, age, and sex in 58 Pima Indians without diabetes.

Another important topic related to the development of CVD is endothelial dysfunction. Enderle et al. (abstract 84) studied 42 patients with type 2 diabetes, showing decreased flow-associated vasodilation using high-resolution ultrasound, with improvement after a 3-month period of treatment appearing more closely related to cholesterol and blood pressure than to glucose lowering. Mather et al. (abstract 585) administered an antagonist to endothelin-1, the most potent locally produced vasoconstrictor, showing similar increase in endothelium-dependent methacholine-stimulated vasodilation in nondiabetic obese and diabetic individuals, with the agent bringing the responses of both groups to the nondiabetic nonobese control level.

Mirzamohammadi et al. (abstract 586) reported that L-carnitine, needed for mitochondrial free fatty acid transport and oxidation, improved methacholine-stimulated vasodilation in obese and normal subjects administered free fatty acids. Finally, Yonaha et al. (abstract 622) measured the change in left ventricular ejection fraction induced by dobutamine, as an index of contractile reserve, and coronary flow reserve, an indicator of coronary microvascular function, showing a positive correlation between the two measures, with both decreased in 20 patients with type 2 diabetes.

References

1. Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, Deychak Y, Simoons ML, Califf RM, Topol EJ, Ross AM: Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-1 experience. *J Am Coll Cardiol* 28:1661-1669, 1996
2. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilehto J: Impact of diabetes on mortality after the first myocardial infarction: the FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 21:69-75, 1998
3. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt

- C, Deanfield J, Conti CR: Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 95:2037-2043, 1997
4. Topol EJ, Nissen SE: Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 92:2333-2342, 1995
5. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434-444, 1993
6. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977-986, 1993
7. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837-853, 1998
8. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57-65, 1995
9. U.K. Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 317:703-713, 1998
10. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 351:1755-1762, 1998
11. Staessen JA, Thijs L, Gasowski J, Cells H, Fagard RH: Treatment of isolated systolic hypertension in the elderly: further evidence from the Systolic Hypertension in Europe (Syst-Eur) trial. *Am J Cardiol* 82:20R-22R, 1998
12. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614-620, 1997
13. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E, the

- CARE Investigators: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 98:2513–2519, 1998
14. ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. *JAMA* 268:1292–1300, 1992
15. The Heart Outcomes Prevention Evaluation (HOPE) Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE study. *Lancet* 355:253–259, 2000
16. U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
17. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. *JAMA* 281:1291–1297, 1999
18. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the Nurses' Health Study. *Am J Epidemiol* 145:614–619, 1997
19. Karason K, Lindroos AK, Stenlof K, Sjostrom L: Relief of cardiorespiratory symptoms and increased physical activity after surgically induced weight loss: results from the Swedish Obese Subjects study. *Arch Intern Med* 160:1797–1802, 2000
20. Lean ME, Powrie JK, Anderson AS, Garthwaite PH: Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 7:228–233, 1990
21. Eriksson KF, Lindgarde F: No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmo Preventive Trial with diet and exercise. *Diabetologia* 41:1010–1016, 1998
22. Chaturvedi N, Fuller JH: Mortality risk by body weight and weight change in people with NIDDM: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetes Care* 18:766–774, 1995
23. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, Weiss SR, Crockett SE, Kaplan RA, Comstock J, Lucas CP, Lodewick PA, Canovatchel W, Chung J, Hauptman J: Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study. *Diabetes Care* 21:1288–1294, 1998