American Diabetes Association Annual Meeting, 1999

More on cardiovascular disease

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This is the final report on the American Diabetes Association (ADA) Annual Meeting and Scientific Sessions held in San Diego, California, in June 1999. It covers topics related to cardiovascular disease, carotid atherosclerosis, and the relationship between type 2 diabetes and inflammation.

Cardiovascular Disease

At the ADA Annual Meeting, Barbara Howard, Washington, DC, delivered the first Edwin Bierman Memorial Lecture. During her presentation, she asked whether, particularly for women, diabetes is the most important cardiovascular disease (CVD) risk factor. There has been a decreasing CVD rate in the U.S. since the early 1960s, but now there is evidence of an increasing prevalence of CVD among women and Hispanic men. The prevalence of diabetes has increased over the past 3 decades in all age-groups, and it has doubled in African-Americans, tripled in Hispanic Americans, and reached astronomical proportions in Native Americans. In virtually all of the populations studied, CVD rates among men and women with diabetes are 2- and 3-fold higher, respectively, than those among individuals without diabetes. The Minnesota Heart Study (1) showed that the prevalence of diabetes among patients with myocardial infarction (MI) increased from 8.2 to 16.8% among men and from 16.0 to 25.8% among women between 1970 and 1985. Howard provided data showing that the frequency of diabetes increased from 26 to 31% among patients who underwent coronary artery bypass grafting (CABG) and that 50% of the women who have undergone an angioplasty have diabetes. Of cases of MI among older adults, 13% are attributed to diabetes compared with 27% to hypertension, but, Howard explained, "it's more than that," with diabetes having many further effects. Cholesterol and blood pressure levels are decreasing in both men and women (2), and cigarette smoking is becoming less common. The Strong Heart Study data show that from 1989–1991 to 1993–1995, the prevalence of triglyceride levels >200 mg/dl among Native Americans with diabetes aged 50–75 years increased from 26 to 28% and from 20 to 23% among women and men, respectively (3). Even a higher prevalence of low HDL and high LDL cholesterol levels has been reported. In this setting, it is understandable that heart disease mortality among individuals with diabetes has increased, even as the prevalence of these incidents has decreased among those without diabetes (4). Not only, then, is diabetes increasing in prevalence, but the prevalences of both CVD and CVD mortality are increasing among diabetic patients. The Strong Heart Study followed 4,500 individuals aged 45–74 years; of these patients, half had diabetes. Diabetes was infrequent among Native Americans before the mid-1960s. Currently, the prevalence rates of CVD mortality among Native Americans in the Dakotas are twice as high as those in the remainder of the population, and similar data have been reported in Oklahoma and Arizona. Compared with the Atherosclerosis Risk in Communities (ARIC) Study, CVD incidence rates are twice as high among Native Americans in the Strong Heart Study. In this population, >75% and >50% of the cases of CVD in women and in men, respectively, are attributed to diabetes. Similarly, there are higher rates of carotid intima-medial thickening in the Strong Heart Study compared with the ARIC. Thus, "as the years go on and the burden of diabetes increases, the [improvement] in CVD will actually turn around and go up." When asked whether she attributed CVD among individuals with diabetes to the elevation in blood glucose levels, Howard pointed out that "you find a significant independent effect of diabetes above and beyond the [other] risk factors." She acknowledged that "glucose per se is a weaker factor."

John D. Rutherford, Dallas, TX, discussed acute ischemic syndromes in diabetes. Atherosclerosis occurs earlier and is more prevalent with diabetes, which frequently coexists with other modifiable risk factors. Important clinical parameters in patients with acute coronary disease include the presence of diabetes, age, a history of prior MI, and cardiomegaly or congestive heart failure (CHF) as shown by an X-ray. Anterior MI and hypotension after the acute event have additional short-term prognostic importance. Rutherford referred to data showing that the prevalence of 1-year mortality among individuals without acute MI who were hospitalized for acute anginal symptoms and were with vs. without diabetes was 25–28 vs. 10–14%, respectively; of these patients, 9 vs. 3% and 17 vs. 9% died within 3 and 12 months, respectively, after hospitalization for unstable angina (5). In Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, 5,944 patients with diabetes and 24,888 without diabetes showed an 11.3 vs. a 5.9% 30-day mortality after MI (6). After non–Q wave MI treated with angioplasty, the event-free survival rate at 1 year was 33 vs. 45% (7). Miettinen et al. (8) reported a 14 vs. 9% and a 22 vs. 8% 28-day mortality prevalence among men and women with vs. without diabetes after MI.

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Abbreviations: ACEI, ACE inhibitor; ADA, American Diabetes Association; ARIC, Atherosclerosis Risk in Communities; CABG, coronary artery bypass grafting; CAC, coronary artery calcification; CHF, congestive heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; DIGAMI, Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; IGT, impaired glucose tolerance; IMT, intima-medial thickness; IRAS, Insulin Resistance Atherosclerosis Study; MI, myocardial infarction; PAI, plasminogen activator inhibitor; PTCA, percutaneous transluminal coronary angioplasty; QTc, corrected QT; TNF, tumor necrosis factor; UKPDS, U.K. Prospective Diabetes Study; WHR, waist-to-hip ratio.

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

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Analysis of some 60,000 patients (10–20% had diabetes) with and without lytic treatment showed at 35 days that 37 vs. 15 lives, respectively, would be saved per 1,000 lytic-treated patients with vs. without diabetes (9). However, in clinical practice, lytic treatment is less frequently administered to patients with diabetes. In the Israeli Bezafibrate Prevention Study, 8,586 subjects without diabetes and 2,318 patients with diabetes had a 26 vs. an 18% 5-year mortality prevalence with vs. without aspirin treatment (10). A 45% event reduction among patients with diabetes who were treated with β-blockers was also documented (11). Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-3) (12) showed that lisinopril treatment within 24 h of MI reduced the 6-month mortality prevalence from 8.1 and 16.1% among patients without and with diabetes, respectively, to 8.1 and 12.9%.

Rutherford pointed out that angioplasty is less effective than CABG in diabetic and nondiabetic patients (34 vs. 3%, respectively, require additional intervention the following year). In the Bypass Angioplasty Revascularization Investigation, patients with diabetes had 65.5 vs. 80.6% 5-year survival prevalence after angioplasty vs. CABG (13). The 9-year National Heart, Lung, and Blood Institute registry data on angioplasty (14) showed a 9-year mortality prevalence of 35.9 vs. 17.9%, a 9-year nonfatal MI prevalence of 29.0 vs. 18.5%, the performance of bypass surgery in 36.7 vs. 27.4%, and the administration of repeat percutaneous transluminal coronary angioplasty (PTCA) in 43.7 vs. 36.5% of diabetic and nondiabetic patients, respectively. Weintraub et al. (15) showed greater efficacy of angioplasty among patients with diabetes in a retrospective analysis, but insulin-requiring patients still had a 35% greater risk with angioplasty than with CABG. The use of an internal mammary graft for CABG is particularly important in demonstrating the advantage of this procedure over angioplasty. This has led to assessment of new approaches for use of angioplasty. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina Study (16) analyzed the platelet glycoprotein IIb/IIIa receptor blocker abciximab in unstable angina. The results showed that the 30-day mortality prevalence, the frequency of MI, or the frequency of needing intervention decreased from 15.9 to 11.3%, with a particular decrease in MI after angioplasty. Treatment was particularly effective with elevation in troponin-T levels, which is suggestive of MI (17). The Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade Study showed, however, that postangioplasty restenosis rates were considerably higher among individuals with than without diabetes and that more patients with than without diabetes required CABG after angioplasty (18).

Thus, diabetes is a major risk factor for acute coronary events, and fibrinolysis is important for patients with diabetes. Early use of ACE inhibitors (ACEIs), β-blockers, and aspirin are crucial. After angioplasty, diabetes is associated with increased short- and long-term mortality. IIb/IIIa Inhibitors do not eliminate the need for revascularization, and stents "help to make the patient with diabetes look more similar to nondiabetics." In diabetes with multivessel disease, CABG is preferable to angioplasty. Rutherford noted that in longer-term studies, restenosis is seen with stents. When asked about the sulfonylureas, he stated "the problem is somewhat murky." A recent study has shown increased mortality with these agents (19), suggesting the need for "major prospective studies" to address this question.

Claus Mamlberg, Stockholm, Sweden, discussed the effect of insulin in the acute MI setting in patients with diabetes. The increased mortality with diabetes after MI, even with lytic treatment, is due to a number of chronic factors: more widespread coronary disease, cardiomyopathy, autonomic neuropathy, and increased thrombogenicity. However, in the acute setting, there is evidence of stress-related insulin deficiency and resistance, increased free fatty acid levels, and increased β oxidation of fatty acids in the myocardium. Fatty acid utilization requires more oxygen, and its intermediary metabolites are toxic; as a result, the ischemic myocardium benefits from glucose metabolism. Pump failure is the most common cause of death in diabetic patients who experienced MI, even though diabetic patients have similar or smaller MI areas than nondiabetic patients. Reinfarction is a second factor. These considerations suggest that protection with insulin of the remaining myocardium is crucial, because it promotes glucose utilization and performs other beneficial actions, such as reducing levels of plasminogen activator inhibitors (PAIs). Thus, the hypothesis of the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study was that improved glycemic control with insulin would improve the prognosis (20). Patients with blood glucose levels >11 mmol/l were randomized to control vs. insulin-glucose infusion for at least 24 h, followed by multidose subcutaneous insulin regimens with thrombolysis in 48% of each group, β-blockers in 68% of each group, ACEIs in 28 vs. 33%, and aspirin in 79 vs. 81%. Of diabetic patients with acute MI, 314 were randomized to the control group and 306 were randomized to insulin infusion. There was a history of prior MI in 37 vs. 40%, oral agents were used for treatment in 37 vs. 46%, and baseline HbA_{1c} values were 8.0 vs. 8.2% in the control and insulin groups, respectively. Blood glucose levels at 24 h decreased from 15.7 to 11.7 mmol/l in the control group but from 15.4 to 9.6 mmol/l in the insulin group. The glucose nadir was seen at 6 h, when 15% of the patients had a level <3 mmol/l. Mamlberg commented that "we were really concerned about those patients, but they did not have harmful effects." The hospital stay was 9.5 vs. 11.3 days, and 43 vs. 87% of patients were discharged on insulin treatment, with 45 vs. 80% and 49 vs. 72% on this treatment at 3 and 12 months. Weight gain at 1 year was 1.0 vs. 1.9 kg. At 3 months, the HbA_{1c} values fell 0.4 vs. 1.1%. Mortality was 26 vs. 18% at 1 year. There was no significant improvement in mortality in patients already treated with insulin, whereas those patients without prior insulin treatment had a decline in mortality of 56% at the time of discharge and of 50% at 3 and at 12 months. The pattern of decline in reinfarction was similar. Risk factors predicting adverse outcomes were age, prior CHF, and blood glucose on admission. In the insulin infusion group, Mamlberg concluded, the adverse effect of hyperglycemia is markedly attenuated, with treatment of 9 patients required per life saved. Among patients who were previously on oral agents, treatment of 7 patients was required per life saved. These findings compare quite favorably with all other CVD interventions. A number of glucose-insulin-potassium infusion studies have been performed in nondiabetic patients with acute MI. A recent meta-analysis of 1,932 patients in 9 trials showed a 28% decline in mortality, which equates to a benefit of 1 life saved per 20 treated patients (21). According to Mamlberg, a glucose-insulin-potassium infusion is an intervention that can "give us time to open the vessels." When asked whether he believed the insulin infusion or the subse-

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quent insulin treatment conferred the benefit in DIGAMI, Mamlberg responded that one cannot tell and that his group is planning a trial to explore this issue.

Rury Holman, Oxford, U.K., described a number of CVD lessons from the U.K. Prospective Diabetes Study (UKPDS). Of the patients enrolled in the study, 22% had MI, cerebrovascular accident, or angina, and 8% died of CVD. Within 10 years, 12% showed clinical evidence of microvascular disease, principally the requirement for laser treatment for retinopathy. The major CVD risk factors in a stepwise multivariate analysis were LDL, then HDL, then HbA_{1c}, then systolic blood pressure, and then cigarette smoking. Holman noted that the study was not designed to treat to a glycemic goal, but rather to analyze 2 differing treatment strategies, immediate vs. delayed, with both sulfonylureas and insulin showing similar 12, 25, and 12% decreases in total and microvascular events and in MI. Metformin caused a greater decrease in macrovascular events than either sulfonylureas or insulin. In the blood pressure substudy, a "treat-to-target" approach was taken, with 5- and 10-mmHg separations in diastolic and systolic blood pressures, requiring at least 3 drugs in 29% of patients. Total diabetic end points, microvascular disease, and stroke decreased 24, 37, and 44%. Thus, for every 1% fall in HbA_{1c} values in the UKPDS, one could expect a 21% decrease in total diabetes end points without evidence of a lower threshold of benefit. Holman acknowledged that "a more aggressive study might achieve a better risk reduction." For MI and stroke, the risk decreased 14 and 12% per 1% fall in HbA_{1c} values and 13 and 13% per 10-mmHg decrease in blood pressure levels without suggestion of lower threshold down to systolic levels of 100 mmHg. There is a suggestion of a microvascular disease threshold of HbA_{1c} values of 7–8%. As HbA_{1c} and blood pressure levels increase, outcomes increase in an additive fashion, so that diabetes mortality per 1,000 patient-years was 8 and 11 in the insulin and control groups with intensive blood pressure treatment and 12 and 19 in these groups with loose blood pressure treatment. The risk gradient for LDL cholesterol was quite steep; MI increased 30% for each 1-mmol/l increase. The Oxford group is now involved in the Lipid in Diabetes Study of cerivistatin plus fenofibrate in a 2×2 factorial design, with anticipated enrollment of ~5,000 patients.

Michael Tuck, Sepulveda, CA, offered another view of the benefits of glycemic treatment in diabetes-related CVD. Hyperglycemia is an independent risk factor for CVD. In the Pathobiological Determinants of Atherosclerosis in the Young Study, of 1,247 young persons who diet, those with HbA_{1c} values >8% showed increased pathologic evidence of coronary atherosclerosis (22). A number of studies from Finland show increased rates of CVD with increasing degrees of hyperglycemia (23, 24). The effect of intensive control is, however, uncertain. There is no definite evidence of CVD benefit in the UKPDS, other than with metformin treatment. Similarly, the Kumamoto Study failed to show a decrease in CVD with tight control. The Veterans Administration collaborative study showed some evidence of increased events with intensive treatment (25). Thus, Tuck concluded, "it is probably unwise to initiate very intensive control with CVD," although the DIGAMI finding of decreased CVD mortality with intensive treatment leaves the question unanswered.

Valmadrid et al. (abstract 62) followed 840 older-onset diabetic participants of the Wisconsin Epidemiologic Study of Diabetic Retinopathy from 1984 to 1996 (abstract numbers refer to the Abstracts of the 59th Annual Meeting and Scientific Sessions of the ADA, *Diabetes* 48 [Suppl. 1]:A1–A550, 1999). Of these patients, 24.8% had microalbuminuria, showing a 1.84-fold increase in CVD mortality, whereas 20.5% had dipstick-positive proteinuria and a 2.61-fold increase in CVD mortality, after adjustment for age, sex, glycemic control, insulin use, alcohol intake, physical activity, CVD history, antihypertensive use, and retinopathy severity. Kerner et al. (abstract 65) reported further on the association between advanced microangiopathy and clinically significant macroangiopathy in 2,439 patients with type 2 diabetes who were treated between 1994 and 1997. Of these patients, 573 had proliferative retinopathy and/or albuminuria >200 μg/min. This group also had a 2.3- to 2.8-fold increase in risk of cerebral or peripheral arterial insufficiency, which was in association with increased triglyceride, cholesterol, blood pressure, and HbA_{1c} levels. In 3,246 individuals from the second National Health and Nutrition Examination Survey who had glucose tolerance testing and were followed for 12–16 years, Saydah et al. (abstracts 68 and 735) analyzed the association between newly diagnosed diabetes and impaired glucose tolerance (IGT). Compared with those subjects who had normal glucose tolerance, the relative risk for all-cause mortality, which was adjusted for age, sex, race, education, BMI, systolic blood pressure, HDL cholesterol, and smoking was 2.75 for individuals with known diabetes, 1.75 for individuals with previously undiagnosed diabetes, and 1.32 for adults with IGT. Of total mortality among women and men in the U.S., 5.7 and 4.5% could be attributed to diabetes. In the Hoorn Study of 2,363 persons aged 50–75 years who were followed from 1990 to 1997, de Vegt et al. (abstract 282) reported that cardiovascular mortality risk associated with 2-h glucose and HbA_{1c} values is more pronounced than that associated with fasting plasma glucose values. Shaw et al. (abstract 734) followed 9,179 persons from Mauritius, Fiji, and Nauru for 5–12 years. Of these individuals, 595 were previously diagnosed with diabetes and 799 were found to have diabetes during the initial screening. Although 243 individuals from the latter group had fasting glucose levels <126 mg/dl, they had 2-h glucose levels >200 mg/dl and showed an increase in mortality similar to the overall group with diabetes. Despite similar time to hospitalization, thrombolysis rates, and treatments with follow-up aspirin, ACEIs, statins, and β-blockers, Kelly et al. (abstract 394) reported that 6-month mortality rates after MI of 33% in 24 patients with diabetes vs. 13% in 73 patients without diabetes. Tian et al. (abstract 545) studied a cardiac GLUT4 knockout mouse model, showing worse diastolic dysfunction after ischemia that did not reverse with reperfusion, a potential mediator of the adverse cardiac outcome after ischemic insult in diabetes.

In a study of the relationship between cardiac autonomic neuropathy and clinical CVD, Poirier et al. (abstract 384) reported echocardiographic evidence of diastolic dysfunction in 60% of men with type 2 diabetes without clinical heart disease. The QTc was 0.45 vs. 0.41 s among nonsurvivors vs. survivors, respectively. Kempler et al. (abstract 643) reported a strong correlation between corrected QT (QTc) and cardiac autonomic neuropathy, based on heart rate responses to deep breathing, standing and Valsalva maneuvers, and blood pressure responses to standing and sustained handgrips in 90 patients with type 2 diabetes. Grandinetti et al. (abstract 720) found insulin resistance associated with increased QTc in 520 individuals screened in the Native Hawaiian Health

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Research Project. Veglio et al. (abstract 389) found that the electrocardiographic QTc was the only significant mortality predictor on a multivariate analysis in a 5-year follow-up of 316 patients with type 1 diabetes. Robinson et al. (abstracts 242 and 527) studied 7 normal subjects during insulin infusion with infusion of glucose, potassium, both, or neither. The QTc increased during insulin administration with euglycemia by 16 and 15 ms with and without potassium, respectively. However, it increased by 53 and 76 ms during hypoglycemia with and without potassium. β-Blockade attenuated QTc lengthening during hypoglycemia without preventing hypokalemia. Russell et al. (abstract 532) showed lesser responses of left ventricular ejection fraction and stroke volume to insulin-induced hypoglycemia in 8 patients with type 1 diabetes compared with 11 control subjects, suggesting an effect of catecholamine or glucagon deficiency. Interestingly, Giunta et al. (abstract 1609) reported that an acute increase in blood glucose levels to 15 mmol increased QTc and blood pressure, pulse, and plasma catecholamine levels in healthy subjects and type 2 diabetic patients.

Carotid Atherosclerosis

At a lecture at the Mount Sinai Diabetes Conference, New York, on 2 December 1999, John R. Crouse, Winston-Salem, NC, discussed the Wake Forest School of Medicine's experience with noninvasive imaging of CVD, particularly in the ARIC Study and the Insulin Resistance Atherosclerosis Study (IRAS). During the 1980s, the prevailing concept was that atherosclerosis was a gradual process involving the narrowing of the lumen with increasing fibrosis and calcification. This concept led to the use of coronary angiograpy in epidemiological studies, which visualized directly the arterial site of greatest interest and had good prediction of outcome. However, coronary disease is only detected at an advanced stage, and Crouse commented that "as soon as people start coming to you asking for help, they really are very different" from general populations. Thus, the development of techniques that can be used in population studies is crucial. Given the strong interrelationships between carotid and coronary atherosclerosis, initial studies used carotid Doppler testing, a technique principally used to identify individuals with >50% stenosis. The Veterans Administration Cooperative Study Group studied >400 men identified by positive carotid Doppler who showed annual coronary event rates of ~4%/year with CHD symptoms and ~3%/year without CHD symptoms (26). Of these patients' first cardiac manifestations, 56% consisted of MI or sudden death. These data stress the potential importance of using noninvasive approaches for patient identification (27). Other studies have showed that even milder degrees of carotid stenosis were predictive of coronary events (28). Salonen and Salonen (29) showed that individuals with 20% more carotid stenosis have a 7-fold increase in risk of CHD events, though with relatively low sensitivity and specificity. Thus, new methodologies were required to assess wall thickening before stenosis. Indeed, analysis of a number of studies have shown that more than two-thirds of coronary events occur in previously nonobstructed vessels (30), suggesting that vessel constriction is a late event, with the artery actually dilating with atherosclerosis, and thereby resulting in lumen preservation until a very late point in the process.

B-mode ultrasound takes advantage of the different acoustic properties of the adventitia and the lumen from the surrounding tissue and the intima, respectively, which allows imaging of the intima-medial thickness (IMT) of both near and far walls. Measurements can be made in the common carotid, carotid bifurcation, and internal carotid. It is not certain that identification of plaques and IMT measurements are the same. In the ARIC Study, 4 communities comprising >15,000 people are being followed; >11,000 of these patients have common carotid IMT ultrasound measurements. At IMT >2 mm, there is a decrease in lumen diameter, but this phenomenon was seen in only <1% of the study population; therefore, carotid lumen narrowing is actually a late event. The common carotid lumen actually increases in size with age and CVD risk factors, including diabetes. Crouse noted that the internal carotid, in contrast, shows a progressive decrease in lumen size at lower increases in IMT, emphasizing the importance of recognizing variations between different arterial beds. Using common carotid IMT measurements, there is a stepwise increase with increasing glycemia (31). The IRAS assessed insulin resistance, glycemia, CVD, and risk factors in >1,000 individuals, including subjects of minority populations, showing the additive effects of high LDL cholesterol, low HDL cholesterol, and hypertension with diabetes on IMT. Other risk factors associated with increased IMT include increased abdominal fat, insulin resistance, passive smoking, dietary saturated fat, psychosocial stress signs, such as anger and latent hostility, and social inequity. Estrogen treatment of women and aspirin use protect against increasing IMT. In clinical trials, regression, or decreases in progression of IMT, can be demonstrated with lipid-lowering treatment.

Chambless et al. (32), in a prospective follow-up of the ARIC Study population, showed that increasing IMT is definitely predictive of increasing CHD incidence rates. At an IMT <0.6 mm, event rates in men and women were 3 and 0.6 per 1,000 events per year, respectively, and increased to 6.5 and 3.4 at an IMT of 0.7–0.8 mm and to 12.9 and 11.7 at an IMT >1.0 mm. Furthermore, individuals who have CHD have more rapid progression of IMT, and, conversely, each 0.03-mm annual increase in IMT is associated with a 2.2-fold increase in relative risk of death by MI or CHD and a 3.1-fold increase in risk of total CHD events (33). A new approach involves imaging of plaque and the arterial wall, with hypoechoic plaques being particularly "vulnerable" and the combination of stenosis and hypoechoic plaque being particularly associated with CVD event risk. A problem with carotid B-mode ultrasound is that it is operator-dependent and requires extensive training. Thus, other noninvasive approaches, such as ultrafast computerized tomography coronary artery calcification measurements, are also being studied. These methodologies do offer the promise of allowing repeated measurements to be performed during the course of the atherosclerotic process with the potential of developing improved treatment approaches for patients with diabetes and other states of increased CVD risk.

Abnormalities in carotid IMT received a great deal of attention in studies at the ADA Annual Meeting. Bonora et al. (abstract 536) followed 826 individuals aged 40–79 years with carotid ultrasound examinations at baseline and 5 years. Although there was little association of diabetes or IGT with early nonstenotic atherosclerosis, the strongest predictors of the development of advanced stenotic atherosclerosis were diabetes, with a 5.2-fold increased risk, and IGT, with a 2.7-fold risk. Fibrinogen, antithrombin III, factor V Leiden mutation, lipoprotein(a), smoking, and alcohol use also predicted advanced disease, whereas hypertension and dyslipi-

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demia predicted early but not advanced atherosclerosis. Sanke et al. (abstract 542) treated 8 type 2 diabetic patients with IMT >1.1 mm of either or both carotid arteries with the antiplatelet agent Beraprost 60–120 μg daily for 4 years and compared them with 16 untreated patients with similar baseline findings, showing a decrease IMT of 0.133 mm vs. an increase of 0.179 mm in the control group. Hanefeld et al. (abstract 550) studied 569 subjects without known diabetes aged 40–79 years. Of these patients, 500 had fasting glucose levels <7 mmol/l and 2-h glucose levels <11.1 mmol/l, 31 had fasting but not 2-hour glucose, 22 had 2-hour but not fasting glucose, and 16 had both fasting and 2-h glucose exceeding these limits. IMT was significantly increased only in the 2 groups with increased 2-h glucose levels; age, male sex, 2-h glucose, fasting proinsulin, total cholesterol, and albuminuria, but not fasting glucose, were independent predictors. Mykkanen et al. (abstract 747) reported that insulin-resistant but not insulin-sensitive offspring of patients with diabetes had increased carotid IMT. Tagawa et al. (abstract 1612) reported that 27 of 82 patients with IMT >1.1 mm vs. 3 of 32 patients with IMT <1.1 mm had macrovascular events over a 5-year follow-up. Nishizawa et al. (abstract 1613) found that the mean IMT was 0.73 mm in 300 healthy subjects, 1.03 mm in 309 patients with diabetes, 1.12 mm in 222 patients with end-stage renal disease, and 1.35 mm in 66 patients with both diabetes and renal insufficiency. Hsueh et al. (abstract 1636) found the degree of insulin resistance to be an important determinant of carotid IMT in 99 nondiabetic adult offspring (aged 18–55 years) of Mexican American patients with documented CAD. Addressing another method of noninvasive CVD assessment, Olson et al. (abstract 185) used electron beam tomography to measure coronary artery calcification (CAC) in 244 type 1 diabetic patients, 37 of whom had CAD, in the Pittsburgh Epidemiology of Diabetes Complications Study. A calcification score >400 was present in ~50% of those patients with CAD but in only ~5% of those without clinical disease. Colhoun et al. (abstract 555) studied 169 patients with and 140 patients without type 1 diabetes. Of both diabetic and nondiabetic men, 52% had CAC. Similarly, 59% of diabetic women had CAC, but only 21% of nondiabetic women had CAC. Other noninvasive vascular studies of interest include those of Parikh et al. (abstract 557), who measured carotid artery distensibility, and Tabak et al. (abstract 561), who measured aortic pulse-wave velocity.

Type 2 Diabetes and Inflammation

A fascinating symposium reviewed the emerging understanding of the relationship between complications of type 2 diabetes and inflammation. Russell Tracy, Pittsburgh, PA, discussed the association between C-reactive protein (CRP) levels and CVD risk that was shown by the Multiple Risk Factor Intervention Trial (34). The Physicians' Health Study similarly showed the risk of MI to increase with CRP levels within the normal range of <10 mg/l (35). The greatest difference between case and control subjects was seen when samples were obtained <6 months before the event, and the benefit of aspirin was greatest among patients with high CRP levels. Tracy stressed that "these folks are not clinically inflamed," but have CRP levels in the upper normal range. D-dimer, a fibrin degradation product, is a "marker of process" of inflammation also associated with increased CVD risk. He speculated that the vulnerable plaque is an ongoing process with an inflammatory component, of which these parameters may be markers, and may be associated with catastrophic rupture. Factor analysis of epidemiological studies that consider inflammatory and coagulation variables, BMI, and insulin, blood pressure, and lipid levels shows associations between lipids and vitamin K–dependent factors, which are associated with inflammatory markers, which, in turn, are associated with procoagulant factors. The latter may be responding to the inflammatory process rather than initiating it. In the IRAS, obesity and insulin resistance were both associated with CRP levels (36), and other studies have shown that CRP levels decrease with weight loss, possibly because visceral fat is known to be a rich source of proinflammatory cytokines. CRP was also associated with IGT, blood pressure, and age, but not with cigarette smoking or with increased carotid IMT. Tracy pointed out that CRP "is detecting the [atherosclerotic] disease process, but it is not exactly the same." Estrogen therapy is associated with an increase in CRP levels, and this association may explain the unexpected results of the Heart and Estrogen/Progestin Replacement Study (37). Postmenopausal women with CVD who were started on hormone replacement therapy had relative risks of 1.5 and 1.6 for coronary events and coronary mortality, respectively, during the first year of treatment. During the subsequent 5 years, though, these risks were reduced. Treatment with estrogen alone and with estrogen plus progesterone decrease PAI-1 levels but markedly increase CRP levels (38). An implication of the CRP data is that infections may be initiators of CVD events. There is little evidence of direct infection of endothelial cells, and it is more likely that infections elsewhere at a critical time cause a worsening of the atherosclerotic process, perhaps by increasing tumor necrosis factor (TNF)-α levels, with CRP as a marker. Other inflammatory and coagulant markers are also important; increased serum fibrinogen is another factor associated with diabetes. In the Strong Heart Study, the progression from normal to micro- to macroalbuminuria and that from normal glucose tolerance to IGT to diabetes were independently correlated with the serum fibrinogen (39).

Burton Sobol, Burlington, VT, discussed the relationship between the vasculopathy of type 2 diabetes and PAI-1. There are 2 types of atherosclerotic plaques: stable fibrotic plaques, which may cause chronic stable angina, and "vulnerable plaques," which cause coronary occlusion after acute rupture and release of their lipid contents. PAI-1 is a component of the fibrinolytic system in blood and tissues. When a clot forms in blood, tissue plasminogen activator converts plasminogen to plasmin, which degrades fibrin to dissolve the clot. PAI-1 is the major physiologically important inhibitor of this process. Increased PAI-1 levels are associated with venous thrombosis in otherwise normal individuals, in women during pregnancy, and during a variety of acute and chronic illnesses. Arterial thrombosis is also seen, and young survivors of MI have increased levels of PAI-1 levels >1 year postevent (40). In the ARIC Study, PAI-1 levels are strongly associated with carotid IMT, and, in the IRAS, a similar association appears to explain the relationship between proinsulin and carotid IMT (41). PAI-1 levels are increased in both diabetic and obese patients. Sobol suggested that insulin itself increases PAI-1 levels. In vitro hepatocyte studies show that insulin increases PAI-1 production. In endothelial cells, PAI-1 production increases in response to glucose. The effect of insulin on PAI-1 is seen in a variety of animal models, and, in humans, endothelial cell mRNA for PAI-1 increases with insulin treatment, whereas both metformin

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and the thiazolidinediones decrease PAI-1 levels. Coronary artery atherectomy specimens show increased PAI-1 in patients with diabetes, in parallel to the changes in blood levels. Increased tissue PAI-1 has been shown to inhibit smooth muscle cell migration into plaques, tending to increase relative lipid and foam cell content, and increasing plaque vulnerability to rupture. Lipid-lowering studies show decreases in event frequency of 25–75%, despite minimal decreases in coronary stenosis, which suggests the benefit of "rendering plaques more stable."

Maria Schmidt, Port Alegre, Brazil, discussed further data from the ARIC Study on the relationship between markers of inflammation and type 2 diabetes. The "common soil" hypothesis proposed by Michael Stern suggests that common antecedents produce both diabetes and CVD (42). Thus, risk factors for both illnesses include age, cigarette smoking, a sedentary lifestyle, hypertension, low HDL cholesterol, hypertriglyceridemia, obesity, central obesity, hyperinsulinemia, and insulin resistance. In the ARIC, those patients with increased BMI, waist-to-hip ratio (WHR), and insulin were more likely to have hypertension, hyperuricemia, and dyslipidemia. Increased levels of circulating TNF-α are seen in diabetes (43) and obesity; are an inhibitor of insulin-stimulated receptor autophosphorylation; and act both directly in an autocrine/paracrine fashion and indirectly by increasing cortisol, free fatty acids, and leptin. TNF-α and other cytokines, such as IL-6, also decrease insulin secretion, decrease endothelium-mediated vasodilation, and potentially play a role in the atherosclerotic process (44). A number of markers of inflammation were measured in the ARIC Study. Of 12,330 patients, 1,335 developed diabetes over the subsequent 7 years. Comparing the 1st vs. 4th quartiles, the leukocyte count showed a significant increase in the relative risk of 1.9, whereas increased fibrinogen and low albumin showed associations that could be explained after adjusting for BMI and WHR. Factor VIII and von Willebrand factor were risk factors for diabetes among women but not among men. Additional markers of inflammation were measured in a subsample of 610 patients. Comparing with the upper and lower halves of distribution, sialic acid and orosomucoid showed 3.7- and 7.9-fold increases in the risk of diabetes (45). These data suggest that cytokine overexpression, which, in part, is due to obesity, possibly reflects underlying atherosclerosis, infection, or even autoimmunity and may be associated with the development of diabetes. In addition, endothelial dysfunction may play a role (46).

Lewis Kuller, Pittsburgh, PA, discussed the implications of inflammation for the prevention of diabetes and its complications. There is now convincing data that type 2 diabetes includes an inflammatory component, perhaps in part related to obesity and genetic factors. The increases in IL-1, IL-6, and TNF-α levels appear to contribute to the insulin-resistant state and to increases in VLDL and decreases in HDL cholesterol levels. These cytokines arise in part from adipose tissue, with TNF-α inhibiting insulin action at the level of the receptor and at postreceptor sites. The relationship of diabetes with CRP, which is highly correlated with IL-6 and TNF-α, appears to reflect these factors. CRP increases with a variety of measures of adiposity, including increasing waist circumference and directly measured visceral fat. CRP is also associated with hyperinsulinemia, LDL particle size, and HDL levels. However, Kuller explained that "what comes first and whether this is all just a measure of fatness is unclear." Yet, type 2 diabetic patients with positive GAD antibodies also have increased CRP levels. Another potential explanation is seen in the frequent elevation of liver enzymes in type 2 diabetes, which reflects steatohepatitis. Interventions based on this understanding of the association among inflammatory mediators, diabetes, obesity, and CVD include weight loss, (whether with diet, drugs, or surgery), aspirin, and other nonsteroidal anti-inflammatory drugs. When available, they will also include agents that inhibit the action of other cytokines, such as IL-6 and TNF-α, and agents to treat steatohepatitis. Among women in a diet program, greater degrees of weight loss are associated with decreased CRP levels; weight loss is also associated with decreased TNF-α and PAI-1 levels. It is worth noting that prostaglandin E2 inhibits glucose-induced insulin secretion; basal islet cycloxygenase-2 (COX-2) expression is dependent on IL-6 and TNF-α, which suggests that COX-2 inhibitors may have specific benefit. It will be important to investigate whether genetic polymorphisms of the cytokines are related to the risk of developing diabetes for a given degree of obesity.

In a related study at the ADA Annual Meeting, De Luis et al. (abstract 1112) reported that 22 patients with type 1 diabetes and *Helicobacter pylori* infection showed increases in HDL and decreases in lipoprotein(a) levels after treatment with amoxicillin, clarithromycin, and omeprazole. These effects were not observed in patients whose infection was not cured. Krebs et al. (abstract 130) infused triglyceride emulsion and heparin to increase FFA levels from 265 to 3,010 μmol/l in healthy male subjects. PAI-1 levels increased 2.6-fold, which could potentially trigger impaired fibrinolysis in diabetes. Zheng et al. (abstract 184) measured PAI-1 levels in 411 patients from the Diabetes Control and Complications Trial follow-up cohort, showing a 27% increase in patients with vs. without hypertension, regardless of age, sex, HbA_{1c} value, albuminuria, or obesity. Hunter et al. (abstract 599) reported an increase in fibrinogen levels in patients with nephropathy from the same population. Herlihy et al. (abstract 547) compared siblings of patients with type 2 diabetes whose fasting blood glucose levels were <108 and between 108 and 139 mg/dl. PAI-1 levels were 2.4-fold higher in the hyperglycemic group and were correlated with insulin resistance. Pucci et al. (abstract 660) and Yoshioka et al. (abstract 662) studied type 1 and type 2 diabetic patients. Patients homozygous for the 4G allele of the PAI-1 gene promoter, which is associated with decreased fibrinolysis, had an increased prevalence of proliferative retinopathy. Friday et al. (abstract 882) reported that postmenopausal women with diabetes treated with conjugated equine estrogen 0.625 mg daily for 8 weeks showed a decrease in PAI-1 levels, which could potentially decrease atherosclerosis.

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