

International Diabetes Federation Meeting, 1997, and Other Recent Meetings

Atherosclerosis and related topics

ZACHARY T. BLOOMGARDEN, MD

This is the fifth of six reports on the International Diabetes Federation (IDF) meeting held in Helsinki, Finland, in July 1997. It deals with atherosclerosis and related topics. Presentations at several recent meetings in the New York area are also discussed.

At the Mount Sinai Hospital Clinical Diabetes Conference held in New York on 23 April 1998, Henry Ginsberg, New York, NY, discussed the role of dyslipidemia in the insulin resistant state and dietary approaches to its treatment. High levels of LDL cholesterol and low levels of HDL cholesterol are well-accepted risk factors for coronary heart disease (CHD). Ginsberg noted that data from the Paris Prospective Study were among the earliest to show increasing CHD mortality with progression from normal glucose tolerance to impaired glucose tolerance to diabetes (1). Subsequent data from this study show a progressive increase in CHD frequency across quintiles of fasting insulin levels, suggesting the importance of insulin resistance (2). In the Quebec Heart Study, for any fasting insulin level, but particularly in individuals with hyperinsulinemia, high apolipoprotein (apo)B levels were a strong marker for increased CHD risk (3). High triglyceride (TG) levels were an important cardiovascular risk factor as well in the Paris Prospective Study, particularly in individuals with hypercholesterolemia (4). Another correlate of CHD risk is the level of small dense LDL particles (5), perhaps because of their tendency to become oxidized and to penetrate the vessel wall. A physical characteristic

that has received attention is the waist-hip ratio, with markedly increased CHD risk among the 95th percentile of the population for this measure (6). For individuals with diabetes, the level of glycemia appears to be a CHD risk marker (7), although no studies have demonstrated that glucose control per se will itself decrease risk.

Ginsberg explained the association of diabetes with hypertriglyceridemia, pointing out that the VLDL particle, produced in the liver to release excess energy, is the source of adipocyte TG, with VLDL remnant particles, enriched in cholesterol, either recycling to the liver or being utilized for LDL formation. In both the insulin-resistant and the insulin-deficient state, adipocytes release free fatty acids, increasing hepatic VLDL production and leading to hypertriglyceridemia. In addition, the enzyme lipoprotein lipase (LPL) is regulated by insulin, with insulin resistance or insulin deficiency decreasing LPL activity and further increasing TG levels. This phenomenon is particularly marked in the 3–5% of the population with genetic LPL abnormalities. These are the individuals most prone to hypertriglyceridemia if diabetes develops. There is an inverse correlation between TG and HDL levels, with a correlation coefficient of 0.4–0.5 in most studies. Ginsberg attributed this to TG-induced increases in the activity of cholesterol-ester transfer protein, which leads to shunting of HDL₂ particles toward LDL formation, which he described as “short circuiting reverse transport.” Cholesterol-ester transfer protein can also mediate trans-

fer of TG from LDL to VLDL in exchange for cholesterol, contributing to increased levels of small dense LDL particles.

Ginsberg discussed several dietary strategies for managing dyslipidemia. He stressed the importance of hypocaloric diets and increasing exercise levels and reviewed the importance of reduction in total and, particularly, saturated fat levels. Recent proposals to avoid the increase in dietary carbohydrate that is a consequence of such diets by increasing levels of monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids have been somewhat controversial. He showed results of studies of diabetic subjects where increased carbohydrate led to increased glycemia and hypertriglyceridemia in comparison to isocaloric high-MUFA diets (8), although Ginsberg pointed out that there were no “earth-shaking differences.” Further, in these diets fiber was kept constant, removing an advantage often associated with high-carbohydrate diets. In the Diet Effects on Lipoproteins and Thrombotic Activity study, high-MUFA diets were compared with high-carbohydrate diets in 85 individuals selected for having either hypertriglyceridemia, hyperinsulinemia, or low HDL. LDL fell by 7% with both diets, HDL fell somewhat less with the high-carbohydrate diet, and TG fell modestly with the high-MUFA diet and rose modestly with the high-carbohydrate diet. However, TG day-profiles and levels after a fat load were similar in both diet groups (9). Ginsberg concluded by emphasizing that we should not “push fats.”

At the Vascular Biology Working Group meeting held in New York on 15 November 1997, Ira Goldberg, New York, NY, discussed the initiators of the atherosclerotic process and the factors leading LDL cholesterol to bind to arterial wall proteoglycans and other negatively charged binding molecules. Atherosclerosis-prone areas such as branch points of arteries may have increased proteoglycan levels or may be areas of stasis, with increased time for LDL cholesterol to enter the arterial wall. In view of recent data suggesting that certain infectious processes

Zachary Bloomgarden is a practicing endocrinologist in New York City.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; apo, apolipoprotein; ACh, acetylcholine; CHD, coronary heart disease; IDF, International Diabetes Federation; IMT, intimal-medial thickness; Lp(a), lipoprotein a; LPL, lipoprotein lipase; MUFA, monounsaturated fatty acids; TG, triglyceride.

may increase atherosclerosis, it is interesting that inflammation increases proteoglycan production as well as increasing sulfation, leading to a more strongly negative charge.

Postprandial lipemia is associated with CHD and with an increase in remnant particles containing apoB-48 rather than the apoB-100 found in LDL. ApoB-48 includes the amino terminus of the molecule, which appears to mediate binding to the vascular wall. Increased exposure of this portion of the molecule may explain the greater atherogenicity of small dense LDL. LDL may be glycosylated, leading to interaction with alternate receptors and formation of antigen-antibody complexes. Glycosylated LDL does not show increased binding to the arterial wall proteoglycan matrix, and this is also the case with oxidized LDL, which has a more negative electrical charge and therefore may actually show a lower degree of binding to the matrix. Goldberg hypothesized that in the atherosclerotic process, oxidation actually occurs on the vessel wall after lipid particles are bound. Goldberg described an experiment done to determine whether TG-rich plasma was lipogenic. Infusion of TG-rich plasma with lipase in an *in vitro* arterial preparation led to increased arterial permeability, presumably with the hydrolysis products allowing entry of LDL and VLDL remnants.

Howard Weintraub, New York, NY, discussed the clinical mandate for aggressive lipid lowering. In 1996 the cost of CHD in the U.S. was \$66 billion, because of the 1.5 million myocardial infarctions and 500,000 deaths occurring annually. By age 60, every 5th man and every 17th woman has had a CHD event. Almost 100 million individuals in the U.S. have cholesterol levels >200 mg/dl and almost 20 million are eligible for treatment, but fewer than 10% of those without CHD and 30% of those with CHD are actually treated. Of those who are treated, 57% and 85% do not reach recommended lipid goals. Diet and exercise lower LDL levels by only about 5%. Weintraub discussed the concept of "dysfunctional endothelium" in which there are decreased nitric oxide levels, increased angiotensin II, increased inflammatory mediators, and increased oxidative stress. It should further be noted that macrophages themselves synthesize and release angiotensin II. Dysfunctional endothelium is vasoconstricted, with increased platelet and white cell adhesion, increased vascular smooth muscle, increased lipid deposition and uptake, and decreased levels of tissue plasminogen activator and

plasminogen activator inhibitor-1, leading to thrombosis. In this setting, lowering LDL decreases ischemic events. A high-fat meal decreases forearm vasodilatation after 4 h, an effect that can be reversed with angiotensin-converting enzyme inhibitors (ACEI). Thus, lipid-lowering treatment has acute effects on vascular reactivity. It is also important to realize that the majority of myocardial infarctions occur in lesions with <50% stenosis, so that the area of greatest lipid deposition is not necessarily that at greatest risk. Furthermore, hypertriglyceridemia is associated with increased CHD risk because of increased chylomicron and VLDL remnants, increased small dense LDL, decreased HDL, and increased coagulation factors. Particularly in patients with increased LDL levels, mild increases in TG can clearly increase CHD risk.

Adrian Selwyn, Boston, MA, discussed the changes in arterial cellular elements, endothelium, smooth muscle, and macrophages on LDL entry and subsequent oxidation. There is a rapid decrease in nitric oxide levels. This leads to vasoconstriction, an increase in inflammatory mediators and adhesion molecules, and impairment and distortion of membrane anticoagulant substances, including heparan, thrombomodulin, and tissue plasminogen activator. Glycation has similar effects. In atherosclerotic arteries, there is paradoxical acetylcholine (ACh)-induced vasoconstriction, although the vessel still responds to the vasodilatory effects of nitrates. Quenching of free radicals with superoxide dismutase restores normal ACh-induced vasodilatation. There is a negative correlation between serum cholesterol and the vasodilatory or vasoconstrictor response to ACh. When cholesterol levels exceed 220 mg/dl, the switch from vasodilatation to vasoconstriction is seen. This can be reversed by lowering LDL levels with statins and further improved by addition of probucol, perhaps because of its antioxidant effect. If statin treatment is discontinued, within 6 weeks ACh causes vasoconstriction, while rapid LDL lowering with apheresis can restore the vasodilatory response within hours.

A number of studies have shown that ischemia on ambulatory electrocardiography is decreased with statin treatment (10). Decreased angina with statin treatment has been reported in the Scandinavian Simvastatin Survival Study, the Cholesterol and Recurrent Events study, and the West of Scotland Coronary Prevention Study (11). Coronary blood flow increases with prava-

statin treatment (12). In a related area, estrogen treatment in women decreases coronary events after angioplasty, although the restenosis rate is not improved, suggesting that a different process is involved (13). The use of B-mode ultrasound to study brachial artery vasodilatation shows that it is decreased in patients with CHD and in young persons with a positive history of CHD and with other risk factors. The evidence of chronic low-grade inflammation in atherosclerotic endothelium is important. Circulating vascular cell adhesion molecules are increased in patients with atherosclerosis as well as in those with increased lipids, but there are decreases after lipid-lowering treatment (14).

In another presentation to the Vascular Biology Working Group, Carl Pepine, Gainesville, FL, discussed new issues in the pathogenesis of acute ischemia. Because only a minority of acute events occur in chronic fibrotic plaques, the more common problem is acute rupture of the "vulnerable plaque," which has progressed more rapidly and exhibits increased mononuclear cells, increased cytokine expression, a thin cap, and lipid enrichment. These lesions are not obstructive. Tumor necrosis factor- β is expressed at high levels in such lesions, and antibody treatment for this is now becoming available. It may have a role in the acute treatment of ischemia. The vasovasorum may be the site of hemorrhage into the plaque and endothelial wall, initiating plaque rupture. Not all plaque rupture actually causes clinical ischemia. Smaller episodes of rupture and thrombosis lead to formation of the thicker fibrous plaques that are less "active." The role of the arterial wall is important, Pepine commented, noting the decrease in acute events in ACEI trials independent of lipid levels, which suggests a relationship of ACEI treatment to vasodilatation, decreased inflammation, decreased oxidation, and decreased growth factors. Alternatively, ACEI treatment may allow patients to better tolerate episodes of acute plaque rupture via increased thrombolysis, increased collaterals, and other mechanisms. Pepine noted that in a large study, patients with LDL cholesterol ≥ 125 mg/dl had less angiographic progression with ACEI treatment, and he referred to other studies in which these agents restored ACh-induced coronary dilatation, suggesting improved endothelial and microvascular function. It is interesting that cigarette smokers develop vasoconstriction from ACh and show greater benefit of ACEI treat-

ment than nonsmokers. Similarly, patients with LDL ≥ 127 had greater vasoconstriction and greater benefit of ACEI treatment. In animal models, oxidized LDL reduces ACh-induced vascular relaxation. This can be blocked with ACEI in a dose-dependent fashion. A bradykinin inhibitor blocks the protective effect of ACEI, suggesting a role of ACEI in increasing bradykinin levels. Pepine noted that angiotensin receptor blockers may have additive benefit to ACEI, but that there is great variability in the response to this combination, with some patients having marked blood pressure reduction. Pepine concluded, "They work, but be careful!"

At a symposium at the IDF meeting, Johan Herlitz, Göteborg, Sweden, discussed the prognosis of cardiac disease in diabetes. Widespread and distal CHD, cardiomyopathy, and autonomic neuropathy predict poor prognosis in diabetic patients with myocardial infarction. During myocardial infarction, insulin deficiency and high free fatty acid levels are adverse factors. Beta-blockers are particularly beneficial for patients with diabetes, and studies of timolol (15) and metoprolol (16) show that mortality reduction is greater among diabetic patients treated with these agents, which promote glucose rather than fatty acid utilization and decrease heart rate. Thrombolytic agents are also valuable, with mortality among diabetic patients receiving thrombolysis decreasing from 17 to 14%, while that among nondiabetic subjects decreased from 10 to 9% (17). An important warning from the Second International Study of Infarct Survival was that aspirin did not benefit diabetic patients in a dosage of 160 mg daily, suggesting that a higher dose may be required (18). The benefit of lipid treatment was shown in the subgroup analysis of the Scandinavian Simvastatin Survival Study, with the 202 diabetic patients in the study showing a decrease in mortality from 25 to 14% and in overall coronary event recurrence rate from 45 to 23% (19). A role of improvement of metabolic control in treatment of CHD was demonstrated by the multicenter Diabetes Insulin-Glucose in Acute Myocardial Infarction study (20). Patients with blood glucose >11 mmol/l were stratified by risk group and prior insulin treatment to a control group and a group that received intravenous insulin and glucose for the first 24 h after myocardial infarction and were then treated with subcutaneous insulin. A total of 620 patients

were randomly assigned, more than 80% of whom had type 2 diabetes. Those in the insulin group had an average blood glucose level of 7 mmol/l during the first 24 h, and 15% developed glucose levels <3 mmol/l, although most were asymptomatic. Total mortality was 23% lower at 3 months and 29% lower at 1 year, with the group not previously receiving insulin having the greatest benefit. Asked about potential risks of sulfonylureas, Herlitz stated, "We do not have sufficient data." (It should be noted that Mühlhauser et al. have commented that much of the benefit shown in this study may in fact be due to withdrawal of sulfonylureas in patients at risk of recurrent myocardial ischemia [21]). Finally, the Bypass Angioplasty Revascularization Investigation showed that for the 19% of patients randomly assigned to bypass or angioplasty who had been treated for diabetes, there was 35% mortality with angioplasty vs. 19% mortality with bypass (22).

At a debate on the topic of whether specific or general treatment should be applied to manage CHD in type 2 diabetes, Charles Clark, Indianapolis, IN, presented a comprehensive review of the data that "hyperglycemia is the soil upon which CHD grows." Abnormalities such as platelet hyperreactivity and increased fibrinogen, von Willenbrand factor, and plasminogen activator inhibitor-1 levels may explain these findings. Analysis of populations with and without diabetes to correct for risk factors shows that diabetes doubles CHD risk. This was most convincingly shown in the Multiple Risk Factor Intervention Trial, where at every cholesterol level the CHD risk of diabetic subjects exceeds that of nondiabetic subjects two- to threefold (23). Other studies have shown each 1% increase in HbA_{1c} to be associated with a 10–29% increase in risk of CHD. In a study of young people dying from noncardiac causes, pathological findings of atherosclerosis were present at a doubled frequency with HbA_{1c} $>8\%$, and in studies in Munich, Germany (24), and Kuvisto, Finland (25), multivariate analysis showed a similar increase in macrovascular mortality with increased HbA_{1c} levels. The Chicago Heart Study showed that over a 10-year period, there was a progressive increase in CHD risk in individuals with 2-h post-oral glucose blood glucose levels of <160 mg/dl, 160–200 mg/dl, and >200 mg/dl and with diagnosed diabetes (26). Thus, regardless of CHD risk factors, individuals with type 2 diabetes have increased macrovascular dis-

ease risk, even with mild hyperglycemia, and the risk increases with increasing glucose levels. There are some data showing that intensive treatment improves this risk, such as the Diabetes Control and Complications Trial finding that lipid and procoagulant abnormalities were improved by intensive treatment and the findings of the Diabetes Insulin-Glucose in Acute Myocardial Infarction study discussed above.

Markku Laakso, Kuopio, Finland, analyzed similar data but concluded that the treatment of dyslipidemia and hypertension is crucial to CHD prevention. He pointed out that the prediabetic state is associated with hypertension, hypertriglyceridemia, hyperinsulinemia, low HDL cholesterol, and obesity, all of which are risk factors for CHD. The Multiple Risk Factor Intervention Trial demonstrates that these risk factors are operative in patients with diabetes in a fashion qualitatively similar to the way they are operative in nondiabetic subjects. Furthermore, subgroup analyses of the treatment in the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events study shows that cholesterol-lowering treatment decreases CHD risk in diabetic patients (11), and analysis of results from the Systolic Hypertension in the Elderly Program shows that blood pressure lowering is similarly effective in diabetic subjects (27). Laakso concluded that the predominant strategy for CHD prevention in diabetes should be one of treatment of associated risk factors, rather than glycemic control per se. The audience agreed with this analysis. A key pad was used for audience polling prior to the debate, and 36% favored glycemic control and 64% nonglycemic risk factor treatment. After the debate the proportion favoring glycemic treatment was similar, 33%, with 67% favoring risk factor reduction strategies.

In a relevant study Boden et al. (abstract 67) studied nine nondiabetic volunteers. Plasma factors VIIa, VIIC, and VIIC, tissue factor pathway inhibitor antigen, and prothrombin fragment F1.2 (reflecting thrombin generation) all rose during hyperglycemic (11 mmol/l) /hyperinsulinemic clamps but remained unchanged during hyperinsulinemic/euglycemic clamps. (Abstract numbers are from Abstracts of the 16th International Diabetes Federation Congress, Helsinki, 20–25 July 1997, *Diabetologia* 40 [Suppl. 1]: A1–A722.). Hyperglycemia per se appears to activate blood coagulation and predispose to cardiovascular complications. Grant

et al. (abstract 68) found that tissue plasminogen activator antigen levels were 11.2 ng/ml in subjects with type 2 diabetes, 10.7 ng/ml in individuals with impaired glucose tolerance, 9.2 ng/ml in those with normal glucose tolerance but fasting blood glucose ≥ 5.5 mmol/l at screening, and 7.6 ng/ml in those with normal glucose tolerance and fasting blood glucose < 5.5 mmol/l. Similar trends were seen with plasminogen activator inhibitor-1 and factor VII, other hemostatic risk factors that cluster with insulin resistance and may be related to increased CHD risk. Lam et al. (abstract 69) studied genetic and environmental influences on factor VII coagulant activity in 264 type 2 and 78 type 1 diabetic patients and in 143 normal control subjects. High factor VII coagulant activity may contribute to the development of macroangiopathic complications and retinopathy in patients with type 2 diabetes. The frequencies of residue 353 Arg Glu mutation were similar in all groups, but levels were higher in those with type 2 diabetes. On multivariate regression analysis, serum TG was the most significant independent determinant of factor VII coagulant activity levels, contributing to $>25\%$ of the variability in control subjects and diabetic patients. Piatti et al. (abstract 70) measured HbA_{1c}, lipid, and insulin levels, insulin resistance index, waist-hip ratio, and mean blood pressure in 140 individuals with type 2 diabetes, impaired glucose tolerance, or normal glucose tolerance. Multivariate regression analysis showed that hypertriglyceridemia was an independent predictor of elevated endothelin-1 and blood pressure, suggesting a role in the development of CHD in patients with the insulin resistance syndrome. Ruhe et al. (abstract 1649) studied the association of glucose intolerance, TG, and HDL cholesterol with mortality in a population-based 6-year study of 2,484 men and women, aged 50 to 75 years. Dyslipidemia (high TG and low HDL) and abnormal glucose tolerance were independent risk factors for mortality attributed to ischemic heart disease and sudden death.

A number of studies presented at the IDF meeting were relevant to the treatment of dyslipidemia in patients with diabetes. Davies et al. (abstract 1663) followed 239 patients with type 2 diabetes not receiving lipid-lowering agents for 1 year. Those whose HbA_{1c} fell during the year had a fall in cholesterol from 5.83 to 5.54 mmol/l, without change in HDL or TG levels, while those whose body weight fell had a fall in TG from 2.53 to 2.09 mmol/l and an

increase in HDL from 1.10 to 1.17 mmol/l. Lahdenperä et al. (abstract 74) reported effects of hormone replacement therapy. Twelve postmenopausal women with type 2 diabetes were treated with estradiol at a dose of 2 mg/day plus norethisterone acetate at a dose of 1 mg/day for 3 months and then with transdermal estradiol at a dose of 50 μ g/day for 3 months, separated by a 3-month placebo period. HbA_{1c} and TG did not change with either treatment. Total and LDL cholesterol were 5.4 and 3.4 mmol/l with oral treatment, but 6.1 and 4.2 mmol/l with transdermal treatment and 5.8 and 4.0 mmol/l with placebo, suggesting that oral treatment is preferable in women with diabetes. Rubinstein et al. (abstract 1687) treated 142 type 2 diabetic patients with bezafibrate at a dose of 400 mg/day and simvastatin at a dose of 20 mg/day in combination therapy for diabetic dyslipidemia. On simvastatin alone, LDL cholesterol decreased by 29% and TG by 16%, and HDL cholesterol increased by 4.2%. No significant change was seen in lipoprotein a [Lp(a)] or fibrinogen levels. Combination therapy decreased LDL cholesterol by 28% and TG by 40%, and increased HDL cholesterol by 17.6%. Lp(a) decreased by 10% and fibrinogen by 10%. Eleven patients had increased creatinine phosphokinase, which required three to stop treatment. In a related report, Idzior-Walus et al. (abstract 1695) gave micronized fenofibrate at a dose of 200 mg/day to patients with features of the insulin-resistance syndrome. Total cholesterol decreased by $\sim 10\%$ and TG by 30%, with an increase in HDL cholesterol by 15%, particularly in patients with lower baseline insulin levels. Glucose tolerance improved slightly.

Utriainen et al. (abstract 3) noted that skeletal muscle of patients with type 2 diabetes is resistant to insulin-induced glucose uptake. They used labeled 2-deoxy-glucose combined with positron emission tomography to quantitate skeletal muscle and myocardial glucose uptake during a euglycemic insulin clamp in 10 patients and 7 control subjects with normal exercise test and resting electrocardiogram (ECG) results. Although whole body and skeletal muscle glucose uptake were significantly decreased, no significant difference was found in myocardial glucose uptake. Myocardial glucose uptake was positively correlated with the left ventricular wall stress and inversely with ejection fraction and stroke volume. The combination of hyperinsulinemia without resistance to

myocardial insulin action in type 2 diabetes may lead to a local increase in insulin action, contributing to CHD.

De Valk et al. (abstract 107) followed 728 patients with type 2 diabetes not treated with insulin and without evidence of CHD for 24 months. Thirty-four had angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal angioplasty, or sudden unexpected death. These events were independently associated with low HDL cholesterol, elevated systolic pressure or pulse pressure, and higher creatinine, suggesting preventive intervention strategies. Abu-Lebdeh et al. (abstract 110) followed 449 patients with type 2 diabetes and without CHD at baseline for a mean of 11.6 years. There were 216 coronary artery disease events, with baseline glucose, TG, and smoking, but not blood pressure, obesity, Lp(a), or cholesterol, being significant predictors. There were 115 cerebrovascular events, also significantly associated with baseline glucose, blood pressure, and smoking. Millns et al. (abstract 114) analyzed risk factors for 99 strokes occurring in 3,776 individuals with type 2 diabetes in the U.K. Prospective Diabetes Study over a 10-year period. Hypertension, age, and sex were significant factors in multivariate analysis, but not BMI; waist-hip ratio; fasting plasma glucose; HbA_{1c}; total, LDL, or HDL cholesterol; TG; insulin; exercise; or smoking.

John Fuller, London, U.K., discussed the World Health Organization Multinational Study of Vascular Disease in Diabetes. This study shows the continuous relationship of blood pressure to CHD mortality but suggests that there is a threshold of renal morbidity at a systolic blood pressure of 160 mmHg. (28). Both renal and CHD mortality were significantly associated with albuminuria. There is little evidence for the benefits of intervention on these risk factors. The Hypertension Detection and Follow-up Program (29) and Systolic Hypertension in the Elderly Program included substantial numbers of diabetic patients treated primarily with thiazide diuretics, with a 33% fall in CHD mortality among those treated. For renal mortality, captopril has been shown to produce clinical benefit (30). Most other studies have used the surrogate end point of progression of micro- to macroalbuminuria, with uniform evidence of an effect of ACEI. The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus included >500 patients with type 1 diabetes, who showed a 50%

improvement with lisinopril, and even at albuminuria levels of 5–10 and 10–20 $\mu\text{g}/\text{min}$ there was a 20% decrease in progression (31). There was also a 50% decrease in retinopathy progression in this study (abstract 1966). Since albuminuria and blood pressure are highly correlated, the American Diabetes Association and Joint National Commission V current blood pressure goal is 140/90 mmHg (ideally, 130/85), while the St. Vincent recommendation is 140/90 mmHg for age <40 and 160/90 mmHg for age >40. Both underdiagnosis and undertreatment of elevated blood pressure are common. Nielsen et al. (abstract 112) administered ramipril at a dose of 5 mg daily or placebo to 31 type 2 diabetic patients with left ventricular hypertrophy and normal blood pressure and urine albumin excretion. After 6 months, there was echocardiographic regression independent of systemic blood pressure, suggesting an additional role for ACEI in patients with diabetes. Syvanne et al. (abstract 108) compared determinants of severity and extent of angiographic coronary disease in 55 type 2 diabetic and 55 nondiabetic patients. For those with diabetes, the only significant predictor was an inverse relation between atheroma burden and HDL cholesterol, while for those without diabetes smoking, LDL cholesterol, apoE phenotype, and apoA2 were significant, suggesting that conventional risk factors have greater predictive power in nondiabetic subjects than in diabetic patients. Fujimoto et al. (abstract 109) presented a 10-year follow-up of 120 nondiabetic and 54 diabetic Japanese-American men without CHD at baseline. The development of CHD was associated with visceral adiposity as determined by computed tomographic scans of the thorax, abdomen, and thigh to assess body fat distribution, as well as with blood glucose, HDL, TG, and blood pressure, but not with insulin or total or LDL cholesterol levels. Pyralaet al. (abstract 56) presented results of the Helsinki Policemen Study on the risk of cerebrovascular disease. Of 1,124 Helsinki policemen aged 34–64 years without previous stroke and diabetes who were followed for 22 years, 90 had a fatal or nonfatal stroke. Significant risk factors included age, obesity, hypertension, and the degree of hyperglycemia after oral glucose. Hyperinsulinemia was not significant as an independent risk factor after adjustment for obesity. Kallio et al. (abstract 1857) prospectively studied 130 patients with type 2 diabetes and 47 age- and sex-matched

nondiabetic control subjects for 7–14 years. At baseline, 21 of those with diabetes, but only 1 control subject, had peripheral arterial occlusive disease based on an ankle-brachial systolic pressure ratio <0.90. This was associated with age and microalbuminuria in multivariate analysis. Development of peripheral arterial disease occurred in 20 diabetic patients and was associated with age, HDL, and total cholesterol levels in multivariate analysis. Blood glucose, HbA_{1c}, C-peptide before and 6 min after glucagon administration, BMI, sex, and mode of treatment were not significant predictive factors.

Intimal-Medial Thickness

Recent studies with ultrasound have shown that carotid atherosclerosis, expressed as an increased intimal-medial thickness (IMT), correlates with coronary disease. Zaccaro et al. (abstract 113) measured urine microalbumin and IMT in 991 nondiabetic subjects and 450 patients with type 2 diabetes in the Insulin Resistance Atherosclerosis Study. There was a relationship between albuminuria and IMT independent of age, sex, ethnicity, lipid levels, and smoking, although it was partly mediated by systolic blood pressure, suggesting that albuminuria is related to atherosclerosis even at an early stage of the disease process. Yoshimura et al. (abstract 1648) found that IMT and carotid and femoral plaque formation were significantly associated with age and cigarette smoking, and, in nonsmoking individuals with type 2 diabetes, with Lp(a) levels. Tsujino et al. (abstract 1722) studied 200 patients with type 2 diabetes and found that the ACE gene DD genotype was associated with increased IMT and, in those subjects with IMT >1.3 mm, with increased prevalence of myocardial infarction. Hiyoshiet al. (abstract 1776) reported that plasma remnant-like lipoprotein levels, measured by an immunoseparation method with the use of monoclonal anti-apoA1 and anti-apoB, were increased in patients with type 2 diabetes and CHD, although they were not associated with increased IMT. Bessho et al. (abstract 1777) and Watarai et al. (abstract 1779) found an association between insulin resistance, measured in minimal model and euglycemic hyperinsulinemic clamp studies, and progression of IMT in 53 patients with type 2 diabetes. Blood glucose and HbA_{1c} were not significant factors. Kodama et al. (abstract 1781) reported that age, total cholesterol, duration of diabetes, smoking, and plasminogen activator inhibitor-1 antigen were independent risk factors for increased

IMT in 189 individuals with type 2 diabetes or impaired glucose tolerance. Temelkova et al. (abstract 1785) reported that in 470 first-degree relatives of patients with type 2 diabetes, impaired glucose tolerance was associated with increased IMT. Rantala et al. (abstract 1804) studied 261 men and 258 women with hypertension and 259 men and 267 women as control subjects. IMT was significantly associated with age, LDL cholesterol, echocardiographic left ventricular hypertrophy, systolic blood pressure, and cigarette smoking, but insulin levels failed to show significant association in multivariate analysis. Keven et al. (abstract 1824) found increased IMT in 23 nonsmoking individuals with impaired glucose tolerance in comparison with 29 control subjects matched for age, BMI, lipids, and blood pressure.

Frost et al. (abstract 1783) prospectively measured IMT in 106 patients with type 1 diabetes aged ≤ 40 years over a 2- to 3-year period and showed independent association with age, hypertension, and albuminuria, while retinopathy, limited joint mobility, hypercholesterolemia, diabetes duration, HbA_{1c}, and sex did not show significant association in multivariate analysis. Yoshida et al. (abstract 1825) compared 26 individuals with type 2 diabetes or impaired glucose tolerance treated with cilostazol at a dose of 100 mg/day with 27 control subjects. Over a 2-year follow-up period, IMT increased 0.016 in the treated patients vs. 0.70 mm/year in those treated with placebo, suggesting that cilostazol is a potentially useful treatment. Ikebuchi et al. (abstract 1787) measured common carotid, femoral, and popliteal arterial IMT in 32 patients with type 2 diabetes. There was greater arterial thickening as well as stenosis in the lower extremities of those with diabetes, suggesting that measurements at these sites is useful in the assessment of the atherosclerotic process in individuals with diabetes. Hosokawa et al. (abstract 1875) studied lower-extremity arteriosclerosis with color Doppler ultrasonography in 110 diabetic and nondiabetic patients with creatinine >1.4 mg/dl. Of those subjects with diabetes, 62% had abnormal studies, but this was true of only 30% of those without diabetes, confirming the strong association of renal insufficiency with arteriosclerosis in patients with diabetes.

Homocysteine

Robert Allen, Denver, CO, spoke on 13 January 1998, at grand rounds at the Mount Sinai Medical Center, New York, NY, on the

interrelationships between homocysteine and vitamins B6 and B12 and folic acid, commenting "it's as important as cholesterol for vascular disease." The major circulating sulfhydryls are the amino acid cysteine and the free sulfhydryl group on albumin; homocysteine levels are an order of magnitude lower. Because of their reactivity, these groups commonly combine in the circulation. Methyltetrahydrofolate and homocysteine form tetrahydrofolate and methionine, the latter a methyl donor acting as an important precursor in synthesis of purines, nucleotides, and many other biologically important molecules. With folate and B12 deficiency, homocysteine levels increase from 5–10 to 50–100 $\mu\text{mol/l}$, a level at which methionine regeneration becomes sufficient for metabolic requirements. Subclinical deficiencies of these vitamins, as well as of pyridoxine, cause smaller increases in homocysteine. Elevated homocysteine levels have been strongly associated with increased vascular disease, including coronary, cerebral, and peripheral vascular diseases, with potential mechanisms including dysfunction of vascular smooth muscle, endothelium, and platelets and oxidative stress. Graham et al. conducted a case control study of homocysteine levels in relation to vascular disease and showed that the relative risk of vascular disease more than doubled in the top quintile of basal and post-load homocysteine (32). This effect was additive with those of other risk factors, particularly smoking and hypertension. Nygard et al. studied 587 patients with angiographically confirmed coronary disease (33). As homocysteine levels increased, mortality increased progressively over a 5-year follow-up. Finally, in a substudy of the World Health Organization antioxidant study, a strong correlation emerged between mean homocysteine levels and the mortality from vascular disease across a number of populations (34). Allen stressed the need to "replace the correct vitamin," pointing out that although folate deficiency is the most common cause of increased homocysteine levels, deficiencies of vitamins B6 and B12 are also important, particularly in older patients. Increased serum methylmalonic acid is a useful indicator of vitamin B12 rather than folate deficiency. Studies suggest that dietary folate levels should exceed 400 μg and vitamin B6 levels, 2–3 mg daily. Low B12 absorption, usually due to gastrointestinal pathology, is more important than decreased ingestion levels. Several ongoing studies are planned with 2.5 mg folate, 0.4 mg B12, and 25 mg

pyridoxine daily to determine whether vitamin treatment of individuals with high homocysteine levels can prevent vascular disease.

A number of studies reported at the IDF meeting addressed the importance of high serum homocysteine levels as a risk factor for cardiovascular disease in diabetes. Hoogveen et al. (abstract 111) found that serum homocysteine $>14 \mu\text{mol/l}$ is a significant risk factor for ischemic heart disease in type 2 diabetes independent of classical risk factors (odds ratio 2.72), but not in individuals with normal and impaired glucose tolerance. Carlsen et al. (abstract 1823) noted that metformin reduces serum vitamin B12 levels and possibly serum folate. In a randomized controlled study, 60 nondiabetic men with CHD were treated with lovastatin at a dose of 40 mg/day and half were given metformin in doses up to 2,000 mg/day. There was a 7% increase in total homocysteine in association with a 13% fall in vitamin B12 levels at 12 weeks, and 14% increase and 18% falls, respectively, at 40 weeks. Folate and methylmalonic acid did not show significant changes, so the mechanism of this effect is uncertain. Marz et al. (abstract 1674) measured homocysteine in 200 female and male patients with type 1 and type 2 diabetes and in age-matched healthy controls. Homocysteine was 12 vs. 15 $\mu\text{mol/l}$ in women with and without diabetes and 13 vs. 17 $\mu\text{mol/l}$ in men. Among individuals with diabetes the severity of macroangiopathic lesions correlated with increasing homocysteine levels. McCann et al. (abstract 1738) assessed the risk of CHD, mortality, and serum folate levels in patients with type 2 diabetes. Age, sex, TG, folate, and cholesterol were significant risk factors for CHD. Low folate was also a significant risk factor for CHD mortality, with an odds ratio of 1.6, in those with normal cholesterol, but it did not add to the risk in those with high cholesterol. Veronelliet al. (abstract 2144) measured homocysteine levels before and after oral administration of L-methionine at a dose of 100 mg/kg and showed no difference between levels in patients with type 2 diabetes and healthy control subjects. There was, however, a significant correlation between homocysteine level and microalbuminuria. Further, homocysteine levels were increased in patients with vascular complications.

Cardiovascular Disease Predictors

Sasaki et al. (abstract 1729) studied 1,700 patients with type 2 diabetes first seen from

1960–1979 and followed until the end of 1993. Mortality rates in male subjects were 32.1 and 37.6 per 1,000 person-years for nonsmokers and for smokers. Causes of death in smokers differed by presence or absence of proteinuria at entry. In patients with proteinuria, increases in heart disease, cerebrovascular disease, and renal disease were noted, but no increase in malignant neoplasms was observed. Only in those without proteinuria were increases in malignant neoplasms, pneumonia, and bronchitis observed. Connolly et al. (abstract 1764) studied the impact of socioeconomic status on the prevalence of coronary risk factors and CHD in persons with diabetes. Of the most affluent group 19.9% smoked cigarettes compared to 41.1% of the most deprived group. BMI was 28.8 vs. 30.4 kg/m^2 in the two groups. For individuals under 70 years of age, 17.2% of the most affluent group but 31.4% of the most deprived group had CHD, with increased prevalence even after accounting for major risk factors. However, coronary artery bypass graft procedures were undertaken more commonly in the most affluent than in the most deprived group. Lehto et al. (abstract 1802) examined the relationship between glycemic control and CHD mortality in 113 men and 115 women with type 1 diabetes aged 45–64 years. Excluding 51 subjects with urine protein $>300 \text{ mg/l}$ or increased serum creatinine, there were 20 CHD deaths during the 7-year follow up. In multivariate analysis a previous history of myocardial infarction increased CHD mortality 8.0-fold, glycosylated hemoglobin in the highest tertile increased mortality 5.4-fold, and duration of diabetes >16 years increased mortality 4.2-fold after adjustment for cardiovascular risk factors.

Arkkila et al. (abstract 1670) and Kantola et al. (abstract 1805) found prevalence of limited joint mobility, Dupuytren's disease, and shoulder capsulitis of 58, 14, and 10% in 291 subjects with type 1 diabetes and 60, 14, and 22% in 139 subjects with type 2 diabetes. Limited joint mobility and shoulder capsulitis were associated with increased cholesterol in type 1 diabetes. Decreased HDL cholesterol was noted in patients with type 2 diabetes and limited joint mobility. Dupuytren's disease was associated with increased cholesterol and TG in patients with type 1 diabetes and was not associated with change in HDL cholesterol. The authors of the report did not comment on whether the associations were direct or indirect (e.g., related to different degrees of neu-

ropathy or nephropathy). There was no association between HbA_{1c} and Dupuytren's disease. Among patients with type 1 but not those with type 2 diabetes, Dupuytren's disease was associated with approximately a 3-fold increased risk of coronary, cerebral, and peripheral vascular disease.

Valensi et al. (abstract 1811) studied cardiac events in 63 patients with type 1 and type 2 diabetes without end-stage renal failure. Exercise ECG, thallium dipyridamole myocardial scintigraphy, and 48-hour electrocardiogram recording were used to diagnose silent myocardial ischemia in 18 patients, and cardiac autonomic neuropathy was diagnosed with the Valsalva, deep-breathing, and lying-to-standing parasympathetic tests in 26 patients. Major cardiac events occurred in 4 patients, 2 of whom had silent ischemia but all of whom had cardiac autonomic neuropathy, suggesting the greater predictive value of the latter. Gall et al. (abstract 1813) measured corrected QT interval length and QTc dispersion, the difference between maximal and minimal QTc durations, in 328 patients with type 2 diabetes. Forty-four patients died of cardiac causes during 9-year follow-up. This represents 38% of patients with prolonged QT interval compared with 19% of patients with normal maximum QTc. Increased QT dispersion, however, did not indicate increased CHD mortality risk.

Oxidation and Antioxidants

Reunanen et al. (abstract 52) measured serum levels of the antioxidants α -tocopherol, β -carotene, and retinol in 106 patients with type 2 diabetes and 201 control subjects matched for sex and age. High levels of serum β -carotene and α -tocopherol were associated with a decreased risk of type 2 diabetes. Oranje et al. (abstract 71) studied 20 patients with type 2 diabetes and secondary failure of oral antihyperglycemic agents who were started on insulin therapy. HbA_{1c} decreased from 10.5 to 8.0% in association with reduced LDL peroxidation. Eriksson et al. (abstract 916) reported that increased ambient glucose concentration leads to increased embryonic concentration of the glycation agent 3-deoxyglucosone, which is formed from the degradation of fructosamine and fructose-3-phosphate and reacts with proteins to form cysteinyl hemithioacetal adducts and advanced glycosylation end products. This was associated with disturbed embryonic development. Wysocka-Solowiej et al. (abstract 920) showed that moderate doses of oral vitamin

E increased antioxidative phenomena in diabetic pregnant rats and diminished fetal macrosomia and hypoglycemia in their neonates. Szaleczky et al. (abstract 1191) reported increased vitamin E and A levels in well-controlled type 2 diabetes. Bascil et al. (abstract 1604) reported that patients with type 2 diabetes and microvascular complications had increased erythrocyte osmotic fragility, which decreased after 6 months of vitamin E supplementation. However, Sindelka et al. (abstract 1189), reported that vitamin E given orally at a dose of 600 mg daily decreased insulin action, suggesting a potential adverse consequence of this therapy.

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