Consequences of Diabetes

Cardiovascular disease

ZACHARY T. BLOOMGARDEN, MD

This is the third of three articles dealing with the International Diabetes Federation meeting, which was held in Paris, 24–29 August 2003.

Paul Valensi (Bobigny, France) discussed approaches to silent myocardial ischemia in persons with diabetes. Addressing the question of whether it is in fact advisable to detect cardiovascular disease (CVD) in persons without history of myocardial infarction or angina, he noted the poor prognosis of persons with diabetes, whose risk of myocardial infarction in the absence of CVD is similar to that of persons without diabetes and with a prior myocardial infarction. Those having evidence of CVD are at particularly increased risk, with half dying within 8 years (1). One-year mortality after thrombolysis is increased by half in persons with diabetes, and survival of persons without diabetes who have had a second myocardial infarction is similar to that of those with diabetes after an initial event (2). The prevalence at autopsy of high grade and multilevel coronary atherosclerosis in diabetic individuals without clinical coronary artery disease (CAD) is similar to that of persons without diabetes with clinical CAD, both for males and for females (3). In a French multicenter study of 417 asymptomatic diabetic persons with at least two additional risk factors undergoing thallium scintigraphy with exercise or dipyridamole, 162 had positive nuclear study, and of 70 having angiography, 39 were found to have evidence of CAD, a positive predictive value of only 56%. Other studies suggest that approximately one-third of asymptomatic persons with diabetes have a positive screening test, but that only approximately one-third of these have positive results on angiography, suggesting poor correlation between functional and morphological abnormality. Alternatively, Valensi suggested, scintigraphy may actually be more sensitive than angiography to the presence of CAD, noting that there certainly is evidence that an abnormal study is associated with poor prognosis. There is, however, at this time no evidence that assessment of asymptomatic patients improves outcome, although a large study would be needed to demonstrate this. He suggested that screening of persons with risk factors was justified, although acknowledging that with current guidelines the majority of persons with diabetes have evidence of additional risk factors. In the French study, 13% of patients had a major CVD event over mean 37-month follow-up, with those having positive scintigraphy studies having a two- to threefold increase in risk. Patients with events were ~4 years older, more likely to be males, and had higher triglyceride and lower HDL cholesterol, but it was difficult to demonstrate a threshold level. A cost-effective strategy would be to study persons with diabetes duration of at least 5 years having two or more risk factors, or diabetic nephropathy, or peripheral arterial insufficiency (4).

Cardiac autonomic neuropathy (CAN) is associated with poor prognosis, with a recent metaanalysis showing a 3.5-fold increase in mortality in persons with two separate positive tests for CAN (5). The adverse effect of CAN is particularly manifest in persons with evidence of silent ischemia. Age is another important marker; a cutoff of 60 years leads to a higher positive predictive value of positive angiography and a higher rate of major CVD events, which occur in ~33 vs. 13% of those above versus below this age. Positive family history and left ventricular hypertrophy are additional important risk markers.

T. Sato et al. (abstract 1075) studied 107 persons with type 2 diabetes without known CVD, with two electron-beam computed tomography measurements of coronary calcification score, showing a mean increase from 91 by 17 units/year, with the coronary calcification score the only significant predictor of angina or myocardial infarction in multivariate analysis including age, smoking, BMI, blood pressure, HDL cholesterol, HbA1c, and creatinine, suggesting an important clinical role off this study. M. Maggini et al. (abstract 1045) reported a 20% prevalence of macrovascular disease among 9,006 persons with type 2 diabetes at 100 Italian diabetes care units. At 1-year follow-up, 14% of those with and 4% of those without prior macrovascular disease events had had a cardiovascular event (~60% coronary). Rates were similar in diabetic men and women. F.T.J. Wackers et al. (abstract 60) presented data from the Detection of Ischemia in Asymptomatic Diabetes (DIAD) study of 1,124 persons, 561 of whom had adenose Tc99-Sestamibi single-photon emission computed tomography (SPECT) perfusion imaging. Twenty-two percent of SPECT studies were abnormal, without significant predictive effect of BMI, cigarette, HbA1c, blood pressure, albuminuria, lipids, homocysteine, or C-reactive protein (CRP), but with autonomic neuropathy as assessed by the ratio of maximum to minimum heart rate during and after Valsalva showing high correlation. M. Kvaril et al (abstract 1034) and J. Charvat et al. (abstract 1036) found positive SPECT evidence of abnormal myocardial perfusion in 31% of 125 persons with type 2 diabetes who had no electrocardiographic or clinical evidence of ischemia, and with two additional risk factors including hypertension, dyslipi-

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; CAN, cardiac autonomic neuropathy; CRP, C-reactive protein; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; FFA, free fatty acid; GGT, γ-glutamyl transferase; HOMA-IR, homeostasis model assessment of insulin resistance; IKS, insulin resistance syndrome; IL, interleukin; NAFLD, nonalcoholic fatty liver disease; SPECT, single-photon emission computed tomography; TNF, tumor necrosis factor.

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demri, cigarette use, family history, or albuminuria. There was no difference between those with and without silent ischemia in age, fasting glucose, HbA1c, or C-peptide. Silent ischemia was associated with higher fibrinogen, homocysteine, CRP, and urine albumin and with 80 vs. 52% prevalence of diastolic dysfunction, greater carotid intima-media thickness and prevalence of carotid atheroma, and lower brachial artery flow-mediated dilatation.

S. Genuth et al. (abstract 59) compared the effects of HbA1c ≤8 vs. >8% during the Diabetes Control and Complications Trial (DCCT) and in the post-DCCT Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up period on the finding of coronary artery calcium 5 years after the conclusion of the DCCT. The mean HbA1c group during follow-up did not have a significant effect, while there were significant 2.3- and 2.9-fold increases in risk of scores exceeding 100 and 200, respectively, based on HbA1c group during the DCCT. O. Kalter-Leibovici et al. (abstract 1437) studied 1,043 diabetic men, mean age 59, 88% with type 2 diabetes, with prevalence of total and severe erectile dysfunction, 82 and 43% vs. 56 and 24% among the 289 with and the 754 without CVD, with CVD increasing the likelihood of erectile dysfunction by 85% controlling for age, diabetes duration and control, hypertension, hyperlipidemia, microvascular complications, cigarette smoking, and drug therapy.

Two studies failed to show benefit of intensive glycemic treatment in hospitals. W.E. Plehwe et al. (abstract 677) implemented the Leuven protocol for glucose control of patients in an intensive care unit, reporting maintenance of mean glucose 117 mg/dl, but with 12 of 40 persons requiring >5 days in the intensive care unit dying in hospital (30%), similar to the 11 of 36 (31%) dying during the year before implementation of the insulin infusion treatment protocol. I.C.C. van der Horst et al. (abstract 1053) administered glucose-insulin-potassium (GIK) versus control infusion to 476 vs. 464 persons with acute myocardial infarction undergoing angioplasty, showing no difference in 30-day and 1-year mortality, although GIK was associated with greater mortality in the subgroup with heart failure and with lower mortality in those without heart failure. There was no significant difference between the GIK and control infusions among the 99 patients with diabetes.

There are CVD consequences of the pre-diabetic state. J. Faber et al. (abstract 1064) reported a substudy of 2,841 persons who had measurement of HbA1c in the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) trial of persons with myocardial infarction complicated by heart failure. A total of 495 persons had diabetes, with 18% mortality, without effect of HbA1c after adjustment for age and sex. However, among persons without diabetes, those with HbA1c <4.9, 4.9–5.1, and >5.2% had adjusted mortality of 13, 17, and 22%, respectively, with a 28% increase in predicted mortality per 1% increase in HbA1c. M.F. Saad et al. (abstract 212) reported on findings of the Multi-Ethnic Study of Atherosclerosis (MESA) of 6,811 persons aged 45–84 years without clinical CVD. Comparing those with normal glucose tolerance, IFG, and diabetes, the mean coronary calcium score was 77, 88, and 114 Agatson units and intimal carotid intima-media thickness 1,055, 1,101, and 1,190 µm, respectively.

D.R. Knight et al. (abstract 1056) studied an animal model of sulfonylurea inhibition of cardioprotection from ischemic preconditioning. With versus without a 5-min period of coronary artery occlusion 10 min before a 30-min occlusion, followed by 2 h of reperfusion, the preceding brief occlusion decreased the extent of infarct, with glyburide but not glipizide inhibiting the benefit of the ischemic preconditioning, adding to a large body of evidence that only the former sulfonylurea may exhibit this adverse effect. A. Stirban et al. (abstract 31) reported that ingestion of an advanced glycation end product–rich beverage not containing either carbohydrate or lipid reduced brachial artery flow-mediated dilation in 44 persons with diabetes, suggesting an adverse effect on endothelial function.

Inflammation

John Yudkin (London, U.K.) discussed the relationship between inflammation and CVD. There is a strong relationship between CRP and mortality in the general population as well as in persons with diabetes. The acute inflammatory response involves a cellular infiltrate, resulting in the production of CRP, which is a major circulating protein. Microinflammation, as shown by elevations of CRP to 3–5 mg/l, may represent inflammation within the vessel wall, a process that is associated with atherosclerosis. However, arterial and venous neutrophil myeloperoxidase levels only show a fall across arterial beds in persons with unstable angina, suggesting that other than in this special case the major determinant of inflammation in diabetes is not arterial inflammation. The insulin resistance syndrome (IRS) is associated with elevations of CRP and phospholipase A2, with other features including hyperinsulinemia as well as elevations in proinsulin, plasminogen activator inhibitor 1, triglyceride, small-dense LDL particles, and free fatty acid (FFA), as well as albuminuria and endothelial dysfunction, leading Yudkin to explain that “the new IRS is enormous and includes low-grade inflammation.” Acute phase markers such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and CRP correlate well with the measures of insulin resistance. Markers of endothelial activation are also correlated, so that the acute phase markers may underlie the association of endothelial damage with the IRS. CRP is produced in the liver in response to a number of signals, particularly IL-6. Measuring antibodies to heliobacter pylori, Chlamydia, and cytomegalovirus, there was only weak association, while much stronger association was present with markers of insulin resistance and with central obesity. Adipose tissue venous levels of cytokines show particular increase in IL-6, which is strongly associated with markers of insulin resistance, although there is no increase in TNF-α in adipose venous drainage. The adipocyte, then, appears to be responsible for up to one-third of levels of inflammatory cytokines, particularly in obese persons. Yudkin speculated that proinflammatory cytokines may be at the center of the processes underlying the IRS, having effects on proinsulin-insulin conversion, on endothelium in various tissues, on coagulation, and on multiple additional abnormalities of the IRS and potentially underlying the association between insulin resistance and vascular disease. Central obesity, physical stress, myocardial infarction, infection, reduced physical activity, and perhaps advanced glycation end products may all stimulate proinflammatory cytokine production. Another important fat-derived molecule is adiponectin, acting as a negative regulator
of insulin resistance. Clearly, then, weight reduction would appear to be an important treatment for the inflammatory state. Rates of obesity are increasing in the developing and developed world. The measurement of BMI itself may not suffice in distinguishing risk across populations, as the degree of adiposity varies with different ethnic groups. Weight reduction leads to decreases IL-6, IL-18, and CRP levels and to an increase in adiponectin. In high doses, aspirin affects nitric oxide (NO)-dependent endothelial vasodilation, not via cyclooxygenase, while low-dose aspirin is not effective in decreasing CRP levels, although being of benefit in decreasing CVD events. Indeed, in the Physicians Health Study, aspirin was effective in people with high but not with low CRP. It did not lower CRP per se but rather was a marker of persons who would benefit from treatment. There have been similar findings for statin treatment, with lovastatin showing particular benefit in persons with low LDL if CRP was high but not in those with low levels.TZDs do appear to lower CRP, with Yudkin showing a study comparing persons randomized to 0, 4, or 8 mg rosiglitazone daily, with active treatment decreasing matrix metalloproteinase and CRP levels, although not associated with change in IL-6. The Leuven intensive care unit insulin therapy study showed marked decrease in mortality, sepsis, renal insufficiency, and peripheral neuropathy, with significant decreases in CRP levels, suggesting that this may be a factor.

M.T. Schram et al. (abstract 118) presented analysis of the EURODIAB Prospective Complications study of 543 persons with type 1 diabetes, showing that a combined inflammatory marker score, based on CRP, TNF-α, and IL-6, was associated with albuminuria, retinopathy, and CVD. L. Tarnow et al. (abstract 951) studied asymmetric dimethylarginine, an endogenous inhibitor of NO synthase, in 408 persons with type 1 diabetes and overt diabetic nephropathy, showing mean levels of 0.40 μmol/L in normoalbuminuric patients, 0.46 in 364 persons without CVD, and 0.48 in persons with a history of nonfatal myocardial infarction or stroke, suggesting this to be a marker (and perhaps a mediator) of cardiovascular risk.

Oxidant stress

Antonio Ceriello (Naples, Italy) discussed the association between oxidative stress and development of complications in diabetes. The classical scheme has been of insulin resistance leading to hyperglycemia, initially most marked postprandially, in persons developing diabetes. Macrovascular disease is, however, present throughout this process, leading Ceriello to speculate that oxidative phenomena may provide an explanatory link. Overnutrition and decreasing physical activity are occurring worldwide and appear to cause cellular overload with glucose and FFA. When glucose passes through tissues it is transformed to energy in the mitochondria with production of free radicals. “This is the key pathway,” Ceriello said, but only the first event. Free radicals are accompanied by an increase in inflammatory markers, ultimately leading to decreased metabolic insulin response in a variety of tissues and to endothelial dysfunction. In addition, glucose and FFA may in part induce β-cell dysfunction via oxidative stress. Thus, Ceriello suggested that oxidative stress may be central, leading to diabeticogenic effects on the β-cell, on endothelium, and on insulin target tissues. New antioxidant agents may allow approaches to treatment, both decreasing CVD and decreasing the development of diabetes. He concluded by recalling Ovid’s evocative “Gutta cavat lapidem, non vi sed saepe cadendo.” (“A drop carves the rock, not by force but by persistence.”)

Eva Lonn (Hamilton, ON, Canada) reviewed evidence for benefit of anti-inflammatory treatment, agreeing that oxidative stress is a major mechanism of atherogenesis, acting in part by causing endothelial dysfunction.

Vitamin E is thought to be the most potent naturally occurring antioxidant, with vitamin C a water soluble antioxidant that regenerates vitamin E. Vitamin E has been shown to decrease platelet adhesion and aggregation and smooth muscle proliferation. Extensive epidemiologic studies suggest that CVD risk is greater in regions with lower antioxidant intakes, particularly of antioxidant vitamins. Some studies show inverse relationship between β-carotene intake and risk, particularly in male smokers. There is an inverse relationship between α-tocopherol intake and CVD risk in men and women. For vitamin C, the data are less consistent, with the National Health and Nutrition Examination Survey suggesting an association between vitamin C and decreased mortality. The U.S. Nurses’ Health Study and Physicians Health Study and several Finnish studies show decreased CVD risk with vitamin E supplementation of at least 100 IU/day. There are, however, inconsistencies in the epidemiologic data. Some studies have only shown relationship to vitamin E intake from food rather than from supplements, although there is potential bias in that persons taking vitamins or following a diet higher in vitamins may differ in other ways from those not following these approaches.

A number of randomized controlled trials have been carried out. There is some evidence of improved endothelial function with vitamin E supplementation, although the beneficial effect may be lost with prolonged supplementation. Morbidity and mortality trials are limited by the duration of observation of reported being ~4–6 years, while benefit may require longer periods. However, the studies that have been carried out have in general not shown benefit, including the Atherosclerosis Supplementation in Atherosclerosis Prevention (ASAP) study (520 persons) (6), the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SUCRE) (732 persons) (7), the vitamin E Atherosclerosis Prevention Study (VEAPS) (320 persons) (8), the de Waart study (180 persons) (9), the Fang study (40 persons) (10), the HDL Atherosclerosis Treatment Study (HATS) (160 persons) (11), and the Women’s Angiographic Vitamin and Estrogen (WAVE) Trial (423 persons) (12). Furthermore, in the HATS trial the benefit of simvastatin plus niacin was diminished with addition of the antioxidants, in the WAVE trial there was similarly suggestion of loss of benefit, and in the SUGAR trial the measurement of carotid intima-media thickness showed “absolutely no effect of vitamin E.” The SPACE trial from Israel of 196 persons with end-stage renal disease showed a decrease in vascular events with vitamin E treatment (800 IU/day) (13). A variety of other large trials, however, failed to show effect or actually suggested increased mortality with β-carotene in the α-tocopherol and β-carotene (ATBC) trial (25,563 men) (14), the β-Carotene and Retinol Efficacy Trial (CARET) (18,314 persons) (15), and in studies of vitamin E
including the ATBC trial, the Cambridge Heart Antioxidant Study (CHASOS) (2002 persons) (16), the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardiaco (GISSI) (11,324 persons; this trial did, interestingly, show benefit of dietary supplementation with n–3 polyunsaturated fatty acids) (17), the Heart Outcomes Prevention Evaluation (HOPE) Study (9,541 persons) (18), and the Heart Protection Study (HPS) (20,536 persons) (19). Fewer studies are available with vitamin C, Lonn noted, although there was small and insignificant increase in risk in three small studies. Studies particularly addressing persons with diabetes show no benefit in mortality, other vascular outcomes, or microvascular outcomes. The Koupio Study of 944 men aged 42–60 does suggest decreased risk of diabetes with vitamin E. In the HOPE study, baseline inflammatory markers were associated with increased risk of development of diabetes, but there was no difference in the risk of developing diabetes.

The larger Nutrition Intervention Trial in Linxian, China, in 29,584 adults showed some evidence of benefit of selenium (20). Other antioxidants, including superoxide dismutase, probucol, and probucol-like agents, may prove to be useful, and there is some evidence that ACE inhibitors may have antioxidant effects. At present, however, Lonn concluded that there is no benefit of antioxidant vitamin supplement in persons with or without diabetes, although noting that “the available evidence does not, however, refute the oxidative hypothesis of atherosclerosis.”

In a vitamin-related sidelight, a number of authors presented studies of type 1 diabetes prevention with vitamin D. A. Giulietti et al. (abstract 461) reported that in the nonobese diabetic (NOD) mouse, an animal model for type 1 diabetes, a vitamin D–depleted diet doubled the rate of development of diabetes in females and quadrupled the rate in males, supporting epidemiologic studies of effects of vitamin D deficiency and of associations between vitamin D receptor polymorphisms in humans. N. Visalli et al. (abstract 1465) randomized 47 children within 4 weeks of developing type 1 diabetes to calcitriol 0.25 μg/day or nicotinamide 25 mg/kg daily, showing an increase of C-peptide from 0.25 to 0.42 vs. 0.28 to 0.31 mmol/l at 3 months, suggesting benefit in increasing residual β-cell function.

**Magnesium**
M. Rodriguez-Morán et al. (abstract 1766) and F. Guerrero-Romero et al. (abstract 1943) found a negative correlation in 96 persons with BMI ≥27 kg/m² and waist circumference >40 inches between serum magnesium and TNF–α, independent of BMI and waist circumference, as well as of age, homeostasis model assessment of insulin resistance (HOMA–IR), and glucose tolerance status, suggesting that magnesium plays a role in the development of the obesity-related inflammatory response. In a study of 60 persons with serum magnesium =0.74 mmol/l and increased HOMA–IR randomized to MgCl₂ 2.5 g daily versus placebo, magnesium increased from 0.62 to 0.81 vs. decreasing from 0.62 to 0.61 and HOMA–IR decreased 43% vs. increasing 2%, suggesting benefit. I. De Leeuw et al. (abstract 1155) randomized 110 persons with type 1 diabetes and erythrocyte magnesium <2.3 mmol/l to 300 mg Mg++ daily versus no supplement for 3 years. Forty-nine vs. 48 persons completed the study, with erythrocyte magnesium increasing only in the supplemented group, who also showed evidence of improvement in neuropathy and retinopathy.

**Homocysteine**
Ellen Hoogeveen (Leiden, Netherlands) discussed homocysteine as a CVD risk factor. Type 2 diabetes, she stated, is associated with increased CVD risk, which cannot be fully explained by classic risk factors. New risk factors include increased homocysteine, which is present in 5–15% of the population and 25%, with similar effect in the general population. The methylene tetrahydrofolate reductase 677C-T mutation is associated with 30–50% decrease in enzyme activity and a 30% higher homocysteine level. This mutation is present in 5–15% of the population and can be treated with folate supplementation. There is also an inverse relationship between homocysteine and the creatinine clearance. Postulated adverse vascular effects of homocysteine include increased reactive oxygen leading to endothelial dysfunction, proliferation of vascular smooth muscle, and lipid peroxidation. Homocysteine levels exceeding 18 μmol/l are associated with a threefold increase in risk of microalbuminuria compared with levels <10, with each 5-μmol/l increase associated with a 28% higher relative risk of albuminuria. Survival of persons with CVD is inversely related to plasma homocysteine. In a study of 587 persons with angiographically confirmed CAD, there was a 4.5-fold increase in risk among persons with homocysteine >20 μmol/l (23). Similar persons have been reported for persons with and without diabetes with renal disease (24). Hoogeveen reported data from the Hoorn study, similarly showing increased mortality risk with increased homocysteine, with mildly increased homocysteine a twofold stronger risk factor for persons with than for those without diabetes. Independent mortality effects of both homocysteine
and diabetes have been reported in other studies (25). Meta-analysis shows that, after adjustment for risk factors, a 25% decrease in homocysteine, which can be achieved with folate supplementation of 0.5 mg daily, is associated with decreased CHD and stroke by 11 and 19%, respectively (26). In a Swiss study of 205 patients undergoing successful angioplasty randomized to folate versus placebo, restenosis occurred in 20% vs. 38% of patients, suggesting benefit (27).

G.T. Russo et al. (abstract 1118) studied 383 persons with type 2 diabetes and 100 healthy control subjects, showing that age, creatinine, vitamin B12 and folate status, and the methylenetetrahydrofolate reductas C677T polymorphism are the main determinants of homocysteine plasma levels in type 2 diabetic subjects, as in nondiabetic individuals, while diabetes duration, HbA1c, and treatment (with insulin, sulfonylureas, or metformin) and the presence of diabetes complications did not affect homocysteine plasma concentrations. G. Cieslik et al. (abstract 2615) studied 117 persons with type 2 diabetes, showing higher homocysteine in men, with association of homocysteine with waist-to-hip ratio and creatinine in men and with creatinine, age, HbA1c, and LDL but without association with CRP. O. Essais-Bedoui et al. (abstract 2614) reported a significant correlation among homocysteine and dyslipidemia, abdominal obesity in women, and microalbuminuria in 100 persons with type 2 diabetes. B. Gonzalez et al. (abstract 1711) found a positive correlation between homocysteine and CRP in 86 persons with metabolic syndrome. D.J. Stocker et al. (abstract 2658) treated 51 type 2 diabetic persons with rosiglitazone versus metformin, showing similar 0.9 and 1.0% falls in HbA1c but a significant fall in CRP and homocysteine only with rosiglitazone. However, S. Dhindsa et al. (abstract 1944) found higher homocysteine levels in obese nondiabetic than in lean persons and higher levels in males than in females, without effect of troglitazone 400 mg daily or of rosiglitazone 4 mg daily for 6 weeks in 9 and 11 obese persons, respectively.

**Lipids**

T. Goldstein et al. (abstract 755) randomized 56 obese persons with type 2 diabetes to a carbohydrate-restricted diet, starting with 25 g and increasing to 40 g daily, compared with a standard calorie-restricted diet for 3 months. Both groups lost on average 2.5 kg, but HbA1c decreased 2.3 vs. 1.1%. M.E. Daley et al. (abstract 1906) described a similar study of 39 obese type 2 diabetic persons randomized to 60 g carbohydrate or “healthy eating,” showing 3.8 vs. 1.6 kg weight loss with more favorable improvement in the HDL–total cholesterol ratio with carbohydrate restriction, although with similar decline in HbA1c of 0.7 vs. 0.4%. B. Gumbiner et al. (abstract 207) presented an analysis of the 836 out of 4,154 persons in the Scandinavian Simvastatin Survival Study with metabolic syndrome, excluding those persons with known diabetes or fasting glucose ≥126 mg/dl. In comparison to those without metabolic syndrome, total mortality was decreased 39 vs. 31%, coronary mortality 54 vs. 43%, and major coronary events 42 vs. 30%, suggesting particular benefit of statin therapy for this group. L. Masana et al. (abstract 208) treated 342 persons receiving statins who had metabolic syndrome based on the Adult Treatment Panel III criteria with ezetimibe versus placebo, showing 25 and 15% falls in LDL cholesterol and triglyceride versus 4 and 6% falls with placebo, with a trend to increase in HDL cholesterol. L. Simons et al. (abstract 1028) from the same group compared 330 nondiabetic high-risk CHD patients with positive CHD history and statin-treated hypercholesterolemia versus 191 such patients with type 2 diabetes. Addition of ezetimibe 10 mg daily decreased LDL cholesterol by 24 vs. 27% and decreased triglyceride by 12 vs. 16%, with little change in patients receiving placebo, and again with a trend to increase HDL cholesterol. R. Dirani et al. (abstract 2287) presented a retrospective analysis of an electronic medical record patient database from 1999–2001 of lipid levels before and 6–12 months after initiation of rosiglitazone versus pioglitazone in 223 vs. 148 patients, respectively, showing that, adjusted for baseline differences, there was a nonsignificant 15 vs. 17 mg/dl fall in LDL cholesterol with the treatments. B. Fagerberg et al. (abstract 175) administered the AstraZeneca-combined peroxisome proliferator–activated receptor α/γ agonist tesaglitazar to 390 persons with triglyceride >150 and waist-to-hip ratio >0.9 for men and >0.85 for women. The placebo-adjusted decrease in triglyceride was 10, 16, 27, and 37% with doses of 0.1, 0.25, 0.5, and 1 mg daily, with respective increases in HDL cholesterol of 4, 1, 11, and 16%. F.L. Hew et al. (abstract 1765) and C.H. Ng et al. (abstract 1852) reported that a 12-week period of treatment with micronized fenofibrate led to a 48% decrease in triglyceride, 21% increase in HDL cholesterol, 21% decrease in LDL cholesterol, 45% decrease in CRP, 26% decrease in fibrinogen, and 30% decrease in uric acid among 30 persons with diabetes and 49, 18 (increase), 19, 14, 19, and 28% falls, respectively, among 24 persons without diabetes, suggesting beneficial effect on components of the metabolic syndrome as well as on lipids. C. Hernández et al. (abstract 1830) measured lipoprotein(a) in four serum specimens from 70 persons with diabetes collected at 3-month intervals, showing association with triglycerides and albuminuria but with a 31.7% variance, suggesting that a single determination could be inaccurate.

**Nonalcoholic fatty liver disease**

T. Takamura et al. (abstract 361) obtained liver biopsies from 12 patients with type 2 diabetes and measured the degree of steatosis (mean score 2 on 0–4 scale), inflammation (mean score 1), and fibrosis (mean score 1.2), as well as performing cDNA microarray analysis, with results compared with those of nine persons without diabetes with normal liver histology. Of 1,083 human cDNAs measured, 266 were upregulated and 94 downregulated in the patients, with subgroups identified that were associated with the histological changes, steatosis and inflammation appearing to represent similar processes, while fibrosis-related gene changes appeared to be independent. P. Andre et al. (abstract 418) examined the association between serum γ glutamyl transferase (GGT) and development of diabetes in a 3-year follow-up of 4,217 persons, 89 of whom developed diabetes. Among those with GGT in the highest versus lowest quartile, the risk of diabetes among men and women was increased 7.3- and 4-fold, with a significant 4.5-fold increase in risk after adjustment for age, alcohol, cigarette use, physical activity, and BMI. B. Cha et al. (abstract 560) examined 779 persons with negative hepatitis B and C serology and average daily alcohol intake <2 oz, with 370 having evidence of nonalcoholic fatty liver disease (NAFLD) on liver ultrasound study.
32 vs. 66% of those with BMI below and above 25 kg/m². Multivariate analysis showed association of sonographic NAFLD with waist circumference, alanine aminotransferase (ALT), HOMA-IR, triglyceride–to–HDL cholesterol ratio, aspartate aminotransferase (AST), and systolic blood pressure, suggesting that this may be considered a feature of the metabolic syndrome. V.D. Yunuk et al. (abstract 2717) performed abdominal sonography on 183 persons with type 2 diabetes, finding 74% with NAFLD, of whom 4% had AST > 50, 7% ALT > 50, and 12% GGT > 50 IU/ml. M. Sakurai et al. (abstract 561) studied patients with biopsy-proven NAFLD, reporting association of the hepatic steatosis score with indexes of insulin sensitivity, with plasma leptin, and with plasminogen activator inhibitor-1, as well as with the diagnosis of metabolic syndrome by World Healthy Organization criteria, suggesting that this be termed the fatty liver–associated metabolic syndrome. Hepatic inflammation and fibrosis were not associated with measures of insulin resistance. T. Kazumi et al. (abstract 575) reported stronger association of ALT than of AST levels with markers of insulin resistance, including BMI, leptin, insulin, triglyceride, and, negatively, with HDL cholesterol, LDL particle size, and adiponectin.

A number of studies addressed potential treatment of NAFLD. M. Bajaj et al. (abstract 170) measured hepatic fat content with magnetic resonance spectroscopy in 11 patients before and 16 weeks after initiation of 45 mg pioglitazone daily, showing a decrease from 21 to 11%, in association with tripling of plasma adiponectin and decrease in fasting glucose from 180 to 130 mg/dl and HbA₁c from 7.8 to 6.5%, although body weight increased 4% from 83.0 to 86.4 kg. K. Iso et al. (abstract 423) described a study of 18 persons with type 2 diabetes and fatty liver, 10 treated with 750 mg metformin and 8 with 2.5 mg glubride daily for 3 months, with the liver spleen computed tomography ratio, a measure of hepatic fat, increasing from 0.76 to 0.92 vs. from 0.85 to 0.91 with glubride, which is compatible with metformin ameliorating hepatic steatosis. G. Belcher et al. (abstract 840) reported liver function studies in 3,713 type 2 diabetic patients treated for 1 year in double-blind controlled trials with pioglitazone, showing decrease in ALT and GGT by 17 and 18% vs. increase by 4% and decrease by 1% with metformin or glubride. E.B. Marliess et al. (abstract 862) administered metformin 2 g daily to five obese nondiabetic men with nonalcoholic steatohepatitis for 12 months, showing weight loss and decrease in insulin levels and ALT without change on liver biopsy or ultrasound estimate of liver fat. W.H.F. Sutherland et al. (abstract 1,895) administered vitamin E 800 mg daily for 3 months and then 1,200 mg daily for a 3 months or placebo to 56 overweight persons, showing a 36% decrease in ALT without change in glucose, lipids, or CRP levels.

Malignancy and diabetes
A. Ferrara et al. (abstract 216) reported that among 33118 adult women with diabetes in the Kaiser Permanente Northern California Diabetes Registry, age-adjusted colorectal and endometrial cancer rates were 0.62 and 1.06 per 1,000 patient-years, respectively, compared with rates among persons without diabetes of 0.34 and 0.35 per 1,000 patient-years, with adjustment for age, obesity, ethnicity, education, cigarette smoking, and alcohol showing 1.8- and 1.9-fold respective increases in risk of the malignancies. S. Svacina et al. (abstract 2732) extended previous studies, showing a 3.2-fold increase in colon cancer among persons with type 2 diabetes to analyze 103 persons with colon cancer, showing that 41% had hypertension, 15% dyslipidemia, 20% diabetes, and 61% overweight, with 40% having three or more components of the metabolic syndrome. They noted that cancer diagnosis occurred 5–9 years after that of diabetes or metabolic syndrome, suggesting this to be a particularly important group for screening. D.S. Papagiosias et al. (abstract 675) reported that 21 persons with asymptomatic pancreatic cancer were found among referrals for new-onset diabetes to their center over the past decade. These patients typically had greater degrees of hyperglycemia and had CA-19-9 > 300 IU/ml. (Their normal is <37 IU/ml, but a comparison group having newly diagnosed diabetes without pancreatic cancer had levels <50.) J. Damiano et al. (abstract 2029) reported their experience with routine pancreatic imaging by either sonography or computer tomography scan in 115 persons >50 years of age with acute severe hyperglycemia, reporting that six patients had pancreatic adenocarcinomas, one a benign pancreatic tumor, one a metastatic cancer with pancreatic extension, one a neuroendocrine tumor, one pancreatitis, one non-Hodgkin’s lymphoma, two ovarian cancer, and one renal carcinoma.

References