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Complications of diabetes

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This is the last of three reports on the 35th Annual Meeting of the European Association for the Study of Diabetes (EASD) held in Brussels in September 1999. It covers topics related to complications of diabetes.

Treatment of Hypertension in Diabetes

John Yudkin introduced a debate on whether calcium-channel blockers (CCBs) should be used as primary treatment of hypertension in patients with diabetes, asking several questions: Are CCBs contraindicated in patients with diabetes? Are all CCBs equal: dihydropyridine and nondihydropyridine, short-acting and long-acting? How useful are surrogate end points such as blood pressure level (which he reminded the audience is not itself a disease but rather a risk marker) and left ventricular mass? Have the HOT (Hypertension Optimal Treatment) (1) and Systolic Hypertension in Europe (Syst-EUR) (2) studies changed our understanding of this issue, and will the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) (3) have further impact?

Jaakko Tuomilehto, Helsinki, Finland, pointed out that in a population survey of 1,032 hypertensive patients in Finland, 46, 17, and 5% of nondiabetic and 59, 17, and 7% of diabetic patients had blood pressure <160/95, 140/90, and 130/85 mmHg, respectively, suggesting the rather poor efficacy of blood pressure treatment in the developed world and leading Furberg to call the reluctance to use CCBs an "unnecessary controversy" (4). Indeed, the CCB-based HOT study showed decreases in cardiovascular disease (CVD) mortality and overall CVD end points of ~70 and 50% in the group randomized to a diastolic blood pressure goal of 80 rather than 90 mmHg, with the benefit restricted to the diabetic subgroup (1).

Tuomilehto recognized that two major studies suggest that CCBs are detrimental in patients with diabetes. In the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), patients treated with amlodipine developed more angina (4 of 191 vs. none of 189 patients), stroke (10 vs. 4), and myocardial infarction (13 vs. 10) (5); and in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial of 470 patients treated with enalapril or nisoldipine, the case fatality was five times higher with the CCBs (6). These studies, however, exhibit atypical features, particularly in having unusually low event rates in the groups treated with an ACE inhibitor. The nisoldipine case fatality of 13.6% in the ABCD trial, whereas far higher than that of the enalapril-treated group, was only approximately one-half and one-third that in the comparable nondiabetic and diabetic subgroups, respectively, of the Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (FINMONICA) Study (7).

Tuomilehto was an investigator in the Syst-EUR study of patients >60 years of age with blood pressure >160 mmHg systolic and <95 mmHg diastolic. The participants were treated with nitrendipine, with the dose increasing from 10 to 40 mg daily as required and addition of enalapril and hydrochlorothiazide if needed. The monitoring committee stopped the trial at 4 years because of the finding of a 42% decrease in stroke and a 31% difference in overall CVD end points, without increased risk of bleeding, malignancy, or other intercurrent illness. Patients treated with nitrendipine versus placebo had a cumulative 2,435 versus 1,303 individual years of follow-up. They showed a 49–64% decrease in these end points, as well as a 50% decrease in dementia. The trial involved 492 patients with and 4,203 without diabetes. The effects on blood pressure were similar, but the benefit of treatment was greater for patients with diabetes in all CVD categories, with total and CVD mortality decreasing 41 and 70%.

Tuomilehto pointed out that nitrendipine has been shown more effective than ACE inhibitors in decreasing left ventricular mass (8) and that although several dihydropyridine-based studies show increased albuminuria, they did not use adequate blood pressure control, with such a study comparing verapamil with trandolipril showing both agents to similarly decrease albuminuria. He concluded that CCBs effectively lower blood pressure, decrease CVD, and may benefit nephropathy, and that there is insufficient comparative data to know whether they are better or worse than other agents.

Bruce Psaty, Seattle, WA, took the opposite side of the CCB debate, stressing his belief that the efficacy of an agent in lowering blood pressure should not be regarded as being in itself a rationale for its use in patients with hypertension (9). Rather, one must assess the degree of prevention of disease end points. Meta-analysis of effectiveness of low-dose diuretics shows relative risk of stroke, coronary heart disease (CHD), congestive heart failure, and mortality of 66, 72, 58, and 90%, respectively. For β-blockers, these risks are

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Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; AGE, advanced glycation end product; CAC, coronary artery calcium; CCB, calcium-channel blocker; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; HOT, Hypertension Optimal Treatment; MI, myocardial infarction; PDR, proliferative diabetic retinopathy; PKC, protein kinase C; SHEP, Systolic Hypertension in the Elderly Program; Syst-EUR, Systolic Hypertension in Europe; TGF, transforming growth factor; UKPDS, U.K. Prospective Diabetes Study; vWF, von Willebrand factor.

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

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71, 91, 58, and 95%, showing benefits comparable to those of diuretics.

Psaty asked what evidence exists for and against the use of CCBs. The diabetes data for Syst-EUR compares favorably to that from the Systolic Hypertension in the Elderly Program (SHEP) (10), with relative risk ratios for stroke, CHD, CVD, and total mortality of 0.31, 0.43, 0.38, and 0.59 in the nitrendipine study and 0.78, 0.46, 0.66, and 0.74 in the diuretic study. However, Psaty warned, the diabetes data represents post hoc analysis, and there were only 12 and 30 events among the treatment- and placebo-group patients with diabetes in Syst-EUR. He also questioned whether such a placebo-controlled study should even have been performed, stating that "after SHEP, we did not need" to prove that active blood pressure–lowering treatment was required for systolic hypertension. He pointed out that to compare active treatments, randomized controlled trials are required. Reviewing such studies, he stressed that 5 of 235 enalapril-treated versus 25 of 235 nisoldipine-treated patients had myocardial infarction in the ABCD trial, that 14 of 189 fosinopril- versus 27 of 191 amlodipine-treated patients had events in FACET, and that isradipine-treated patients with HbA_{1c} >6.5% had a CVD event ratio of 2.81 over diuretic-treated patients in the Multicenter Isradipine Diuretic Atherosclerosis Study (11).

Psaty showed that analyses carried out by his group in Seattle showed CCBs to cause more CVD events than diuretics or β-blockers. Overall, he pointed out, randomized controlled studies of CCBs versus other antihypertensive treatment modalities have shown relative risks of CVD events to be 3.3- to 6.9-fold higher. In contrast, he pointed to the Captopril Prevention Project (CAPPP) study, which showed increased benefit of captopril over conventional antihypertensive treatment in diabetes (12). In the U.K. Prospective Diabetes Study (UKPDS), captopril and atenolol had similar benefit in patients with diabetes (13), and blood pressure treatment offered greater benefit to patients with diabetes in reducing mortality than did treatment of hyperglycemia per se. He therefore termed blood pressure treatment in diabetes "exceedingly important," but cautioned that he did "not think that we can generalize outside of the trials" to use angiotensin receptor blockers, to use α-blockers, or to use CCBs, which he felt have "compromised evidence" in comparison with ACE inhibitors, diuretics, and β-blockers.

Retinopathy

Using data from 1,441 individuals in the Diabetes Control and Complications Trial, Tabák and Orchard (abstract 34) showed data suggesting that a measurement of cumulative glycemic exposure, calculated as the sum of HbA_{1c} units above normal multiplied by the duration between measurements, was more strongly predictive of proliferative diabetic retinopathy (PDR) risk than HbA_{1c} alone.

A number of studies suggested nonglycemic pharmacological approaches that may play a role in prevention of retinopathy. Fathallah et al. (abstract 37) evaluated lipid peroxidation in the early diabetic retina, showing an increase in free malondialdehyde and 4-hydroxyalkenals that could be prevented by DL-α-lipoic acid. Gilbert et al. (abstract 38) showed that streptozotocin-induced diabetic rats had increased retinal vascular endothelial growth factor expression in the inner vascular network, including the ganglion cell layer and inner nuclear layer, and showed retinal hyperpermeability normalization by administration of the ACE inhibitor perindopril. Li et al. (abstract 1200) reported improvement in ultrasonographic measures of retinal hemodynamics in 105 patients with type 2 diabetes treated for 6 months with captopril versus placebo. Ways et al. (abstract 40) studied 29 patients with type 1 or type 2 diabetes of <10 years' duration and no or minimal retinopathy. Retinal blood flow showed a significant dose-related increase with the protein kinase C (PKC)-b inhibitor LY333531 (0–32 mg daily for 28 days).

Spranger et al. (abstract 35) assessed vitreous fluid from control patients without retinal neovascularization, patients with PDR after scatter laser photocoagulation, and patients with PDR without previous retinal photocoagulation. Angiostatin, a peptide that includes the sequence of the kringle region of plasminogen, is an inhibitor of neovascularization. Angiostatin levels were present in vitreous fluid from 24 of 26 the patients with prior scatter photocoagulation but in only 3 of 24 without previous photocoagulation and 2 of 18 control subjects. This suggested that production of the angiogenesis inhibitor angiostatin in human vitreous is a possible mediator of the positive effects of retinal photocoagulation.

Hitman et al. (abstract 39) showed a polymorphism of the regulatory region of the gene for the advanced glycation end product receptor, with gene frequency differing in 119 patients with PDR and 57 patients with diabetes of at least 15 years' duration without retinopathy, thus suggesting a factor determining susceptibility to PDR. Cantón et al. (abstract 35) found that concentrations of hepatocyte growth factor, an angiogenesis inducer that stimulates proliferation and migration of endothelial cells, were 17.0 and 5.9 ng/ml in vitreous of patients with PDR and patients without diabetes, respectively, suggesting this to be a mediator of neovascularization. It is noteworthy that Ueda et al. (abstract 86) showed that hepatocyte growth factor correlated with BMI in 29 nondiabetic subjects and 78 type 2 diabetic patients, suggesting it as a potential atherosclerosis mediator as well.

Neuropathy and the Diabetic Foot

Rajbhandari et al. (abstract 182), noting the increased mortality of patients with diabetic neuropathy, compared 22 patients with and 29 patients without neuropathy followed for 9 years. HbA_1 was 11.6 vs. 9.7%, cholesterol 5.5 vs. 4.7 mmol/l, and triglyceride 1.6 vs. 1.3 mmol/l. This suggested an association between cardiovascular risk factors and development of neuropathy and was compatible with a vascular etiology for neuropathy.

Walker et al. (abstract 152) studied 10 patients with diabetic amyotrophy with proximal leg weakness and pain for 4 months. Nerve biopsy showed a decrease in myelinated fiber density of the intermediate cutaneous nerve of the thigh and sural nerve with axonal atrophy and unmyelinated fiber regeneration. Tack and Goldstein (abstract 153) studied 9 patients with painful diabetic foot neuropathy without generalized autonomic neuropathy. Positron emission tomography scanning showed a decrease in norepinephrine spillover in the feet, suggesting selective regional denervation of the sympathetic nervous system, which may mediate pain sensation.

Kästenbauer et al. (abstract 99) studied foot ulcer risk factors in 187 patients without history of ulcer or ischemia over a 2-year period. In the group, there were 38.3 foot ulcers per 1,000 person-years, with abnormal vibration perception and forefoot plantar pressure during standing associated with a 14.7-fold increase in risk.

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Armstrong et al. (abstract 101) studied hypertrophic bone formation, which has the potential to cause abnormal foci of high plantar pressure after partial foot amputation. Of 92 subjects, 44.6% of subjects showed >3 mm of bony regrowth on X ray ~2 years after the procedure. This was seen in 58% of the men versus 17% of the women, in 74.2% of the amputations done using manual bone cutting and 29.5% of those using power bone cutting instrumentation, and in 34.1% of those with osteotomy made distal versus 11.8% with osteotomy made proximal to the surgical neck of the metatarsal. The latter two findings suggest important technical approaches to reducing the risk for ulceration, infection, and reamputation. Jirkovská et al. (abstract 102) compared 16 diabetic patients in the early stage of Charcot osteoarthropathy with 30 sex- and age-matched healthy control subjects. The ultrasound heel densitometric T-score was −3.0 vs. −2.4, and the collagen type I cross-linked C-telopeptide level was 8.49 vs. 3.94 ng/ml, confirming active bone resorption and contributing to the increased risk of fracture.

Two studies looked at treatment options for foot ulcers. Pham et al. (abstract 104) studied 16 and 17 patients with diabetes and nonischemic, noninfected diabetic foot ulcers averaging 2.5 cm^2 in area at entry randomized to the human skin equivalent graftskin (Apligraf), a bilayer of keratinocytes and fibroblasts engrafted in collagen (applied weekly for up to five applications), or to saline gauze dressings. Ulcers closed in 39 vs. 91 days, and 12 vs. 7 patients had complete wound closure. Foster et al. (abstract 105) treated 30 patients with neuropathic ulcers present for an average of 45 weeks with an ester of hyaluronic acid to promote granulation tissue formation. A total of 12 of 13 sinus tracts healed with treatment, whereas only 1 of 9 healed in the control subjects; and 10 of 15 ulcers healed with treatment versus 3 of 15 in control subjects.

Lipids

Several studies assessed the effect of treatment with cerivastatin on lipid levels in patients with diabetes. Rubinstein et al. (abstract 244) randomized 256 patients with type 2 diabetes and LDL >3.35 mmol/l plus triglyceride <4.56 mmol/l to cerivastatin (0.1 or 0.3 mg/day) or placebo. LDL cholesterol decreased 20 and 34% with the two doses of cerivastatin, triglyceride decreased 4 and 12%, and HDL cholesterol increased 6% with both treatments. Esper et al. (abstract 243) studied 351 patients treated with cerivastatin (0.3 mg daily), bezafibrate (400 mg daily), or a combination of both. LDL cholesterol fell 21, 35, and 46%; HDL cholesterol rose 25, 12, and 34%; and triglycerides fell 40, 14, and 44%, respectively. Similarly, Farnier et al. (abstract 779) compared 115 patients with hyperlipidemia treated with cerivastatin (0.3 mg daily), 112 treated with fenofibrate (200 mg), and 115 patients treated with both for 16 weeks after a 6-week placebo washout. LDL cholesterol fell 28, 21, and 41%; HDL increased 6, 12, and 12%; and triglyceride fell 10, 31, and 37%. Transaminase elevations were, however, somewhat more frequent with the combination.

Other groups studied the effects of other treatments and combinations with antidiabetic medications. Buter et al. (abstract 1095) reported a fall in non-HDL cholesterol from 3.8 to 3.6 mmol/l and in apolipoprotein B from 0.74 to 0.68 g/l with losartan treatment in 8 patients with microalbuminuria. Cull et al. (abstract 63) reported that chlorpropamide and metformin modestly lowered cholesterol by 0.2 and 0.4 mmol/l and triglyceride by 0.2 and 0.4 mmol/l, with less effect using insulin and glyburide in comparison with conventional treatment, in 2,249 patients treated during the UKPDS. Keenoy et al. (abstract 169) administered vitamin E (750 IU daily) for 1 year to 22 metabolically stable type 1 diabetic subjects. Serum vitamin E increased from 15.9 to 28.6 μg/ml, HbA_{1c} did not change, and copper-induced in vitro peroxidability of LDL and VLDL decreased 15–60%.

Heart Disease in Diabetes

The Castelli Pedroli Prize was awarded on the occasion of the 14th Camillo Golgi lecture to Eberhard Standl, Munich Schwabing, Germany, who discussed "the diabetic 'sweet' heart from ailing to failing." The World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA)-Augsburg registry shows that there has been little progress in survival of patients with diabetes after myocardial infarction (MI), whereas there is improved survival of patients without diabetes. Both the 5-year survival of those who were alive at 28 days and the 1st day mortality show this pattern, although patients with and without diabetes are similar in other risk factors and in size of the infarcted region. Indeed, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Study showed a doubling of the 30-day mortality among patients with diabetes (14). One explanation is the increased risk of congestive heart failure after MI, which is four times greater in patients who have intermediate size MI. Decreased blood flow, decreased glucose utilization, and decreased diastolic compliance are all contributory factors.

Standl showed investigations based on the study of cardiac sympathetic activity with ^{123}I-labeled monoiodo benzyl guanidine single photon emission computed tomography scanning that suggest "cardiac sympathetic incompetence" of patients with diabetes. Normal post-MI remodeling involves neurohumeral activation, which is defective in diabetes. Sympathetic dysfunction is present even without evidence of autonomic neuropathy on the electrocardiogram or of perfusion abnormality on angiography. Standl said that it "is likely to be the key for the diabetic noninfarcted myocardium," explaining the difference in outcome given the similar degree of initial myocardial loss.

Standl hypothesized that resistance to sympathetic nervous system activity exists in diabetes and may develop initially as a protective effect against increased circulating catecholamines. Thus, a particular risk marker is that of the patient whose heart rate fails to increase during exercise. Positron emission tomography scans of myocardial blood flow and measures of endothelium-dependent vasodilatation show defects in both areas in patients with diabetes, for whom "the physiologic stimulatory effect of insulin on nitric oxide seems to be counteracted." Another factor in diabetes is the increase in sudden death in association with the increased QT interval on electrocardiogram, which is more strongly associated with ischemia than with neuropathy. Endothelial activation of angiotensin II, transforming growth factor (TGF)-β, and von Willebrand factor (vWF) represents another set of mechanisms of sudden death in patients with diabetes, with lack of NO appearing to be a crucial contributor to these processes, which in turn potentiate plaque rupture and acute coronary syndrome.

Noting that patients with previously undiagnosed diabetes have an adverse cardiac prognosis similar to patients with known diabetes, with HbA_{1c} a risk factor in type 1 and type 2 diabetes, Standl hypoth-

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esized that HbA_{1c} "needs to be close to normal, a tremendous challenge to our current treatment goals," and showed that near-normoglycemia may partially reverse the sympathetic cardiac dysfunction of patients with diabetes. This may explain the DIGAMI (Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction) study finding of an 11% decrease in post-MI mortality in patients randomized to intensive treatment, with the mechanism appearing to be a decrease in congestive heart failure rather than in reinfarction (15). The recent Excimer Laser Coronary Angioplasty (ECLA) Glucose-Insulin-Potassium trial has confirmed some of these results (16). Some of the sympathetic abnormality may have an immune mechanism, with evidence of antisympathetic neuron antibodies in newly diagnosed type 1 diabetes, which is associated with evidence of autonomic dysfunction. One mechanism of the adverse effect of hyperglycemia is PKC activation, which leads to a decrease in heparan sulfate proteoglycans, inhibits NO-dependent vasodilation, and stimulates formation of cytokines such as vascular endothelial growth factor and TGF-β. The development of PKC-β–specific inhibitors may provide therapeutic approaches to block these pathways. Standl concluded by contrasting evidence that multifactorial intervention can improve microvascular outcome with "the reality in clinical practice" and pointed out both that patients with acute coronary syndrome have an increased rate of developing diabetes and that patients with diabetes most frequently die of cardiac disease. "Better care for the 'sweet' heart of our patients," he affirmed, "should be at the heart of our daily work."

Macrovascular Disease

Rutter et al. (abstract 1208) reported independent associations between the ankle-to-brachial systolic blood pressure index and albuminuria and leukocyte count in 86 patients with type 2 diabetes, without additional contributions of age, sex, blood pressure, cigarettes, obesity, glycemia, fibrinogen, or lipids. Festa et al. (abstract 217) studied the relation of C-reactive protein (CRP) to insulin resistance measured by a frequently sampled intravenous glucose tolerance test in 1,088 nondiabetic subjects free of clinical coronary artery disease in the Insulin Resistance Atherosclerosis Study. CRP correlated with BMI, waist circumference, insulin sensitivity, fasting insulin, and intact and split proinsulin, suggesting that chronic subclinical inflammation is part of the insulin resistance syndrome and that anti-inflammatory as well as insulin-sensitizing treatment may benefit healthy individuals with insulin resistance.

Several studies explored the relationship between cardiovascular changes and albuminuria. Veglio et al. (abstract 212) followed 316 patients with type 1 diabetes and 106 control subjects for 5 years. Having a long QTc interval on electrocardiogram was associated with a 20-fold increase in mortality, which was significant after adjustment for age, diabetes duration, and blood pressure. Diem et al. (abstract 1119) similarly reported a linear relationship between corrected electrocardiogram QT interval and 13-year mortality in 300 patients with diabetes, although the association was significant only for the subset with proteinuria. Knudsen et al. (abstract 215) reported echocardiographic left ventricular hypertrophy in 39% of women and 25% of men with diabetes; the prevalence was associated with greater age, HbA_{1c}, and urinary albumin levels. Berger et al. (abstract 256) reported on the 10-year follow-up of 3,570 patients (1,829 with normoalbuminuria, 1,257 with microalbuminuria, and 367 with macroalbuminuria) begun on insulin treatment before age 31 years. Standardized mortality ratios were 2.2, 3.2, and 11.5 among men and 2.5, 3.5, and 27.0 among women in the three albuminuria groups, with 36, 38, and 60% of deaths caused by cardiovascular disease.

Jager et al. (abstract 258) measured urinary albumin-to-creatinine ratio, plasma vWF, and retinopathy in 173 patients with type 2 diabetes followed for 7 years. The risk of cardiovascular disease was not increased by either albuminuria or retinopathy alone, but was 8.9-fold greater in patients with both findings. Similarly, neither vWF nor albuminuria alone increased risk, but patients with both microalbuminuria and vWF >183% had a 10.9-fold increase in risk, suggesting that the subset of patients with albuminuria and endothelial dysfunction has a particular increase in cardiovascular disease. However, Gæde et al. (abstract 259) did not find an association of vWF with increased CVD risk in 160 patients with microalbuminuria and type 2 diabetes followed for 3.8 years.

Le et al. (abstract 213) followed 209 patients with diabetes for 40 months, showing that individuals with a midtertile electron-beam ultrafast computed tomography scan coronary artery calcium (CAC) score had 9 coronary events, those with the highest scores had 5 coronary events, and those with the lowest scores had 3 coronary events, suggesting that this may be a noninvasive measure of unstable plaques. Colhoun et al. (abstract 214) reported CAC in 52% of men with and without type 1 diabetes, but in 47% of women with type 1 diabetes and 21% of women without diabetes, with evidence of some association with cardiac autonomic neuropathy.

González de Molina et al. (abstract 1070) reported that among 662 consecutive patients, the presence of blood glucose >120 mg/dl on hospital admission with acute MI conveyed a 3.9-fold increase in 28-day mortality risk, regardless of coronary risk factors, cardiac treatment, or prior history of diabetes. In a study addressing treatment of the patient with diabetes with unstable angina or acute MI, Melidonis et al. (abstract 1066) studied 48 type 2 diabetic patients not previously treated with insulin randomized to intensive insulin treatment or conventional management. Tissue plasminogen activator increased similarly from hospitalization to discharge, from 15.4 to 21.2 and from 14.5 to 19.2 ng/ml in the groups with and without insulin treatment. Fibrinogen decreased in the intensive insulin treatment group from 2.9 to 2.7 g/l, while increasing from 3.0 to 3.6 g/l with conventional treatment; and plasminogen activator inhibitor I decreased from 30.8 to 27.8 ng/ml with intensive insulin, while increasing from 30.6 to 40.6 ng/ml with conventional treatment. This suggested improved fibrinolysis with insulin treatment.

Warner et al. (abstract 1055) studied 136 patients of Asian ethnicity in the U.K. undergoing elective coronary angiography—58 with and 78 without diabetes. Despite similar frequencies of cigarette smoking and prior coronary disease history and similar levels of blood pressure, fibrinogen, and cholesterol, the diabetic group had 33 and 36% findings of two- or three-vessel disease. The group without diabetes had 15 and 23% prevalence levels of these findings. There was no coronary disease in 26% of the nondiabetic group but only 7% of those with diabetes.

Glycation

Makita et al. (abstract 996) measured a circulating noncarboxymethyl lysine advanced glycation end product (AGE) and pentosidine, showing a correlation with progression of albuminuria in 18 patients

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with type 2 diabetes. These AGE levels correlated with mean fasting glucose levels over the preceding 3 months, whereas HbA_{1c} correlated more strongly with mean fasting glucose levels over the preceding 1 month. Meerwaldt et al. (abstract 210) reported that a noninvasive measure of skin autofluorescence in diabetic patients was 30–35% higher than that in matched control subjects, showing a correlation with HbA_{1c} and suggesting that this may be a measure of skin AGE levels.

Zhang et al. (abstract 371) reported in vitro AGE-induced tumor necrosis factor-α production of 473 and 254 pg/ml and interleukin-6 production of 2,400.0 and 1,983.9 pg/ml by lymphocytes obtained from 50 patients with diabetes and 55 normal subjects, suggesting an immune response to AGEs in diabetic individuals. Bünting et al. (abstract 206) found that soluble AGE peptides from instant coffee and from cola soda increased expression of vascular cell adhesion molecule 1 and activated nuclear factor-κB in cultured human umbilical venous endothelial cells, suggesting that food AGEs can induce endothelial dysfunction.

Several studies addressed potential mechanisms of AGEs in atherogenesis. Turk et al. (abstract 207) measured anti-AGE antibodies in 20 nondiabetic control subjects, 35 diabetic patients without microangiopathy, and 15 with nephropathy or retinopathy, showing binding inhibition levels of 26.4, 33.5, and 42.0%, correlating with HbA_{1c} levels. Kearney and Sharp (abstract 208) reported that glycated albumin upregulated vascular endothelial growth factor expression.

Psychosocial Complications

Howard et al. (abstract 3) analyzed 13,309 patients with diabetes >45 years of age treated with acarbose, metformin, or a sulfonylurea from a primary care database representing 653 physicians associated with 145 general practices in the U.K. During 1 year of follow up, they found that 50% of those treated with acarbose, 27% of those treated with metformin, and 16% of those treated with sulfonylureas failed to refill their oral antidiabetic prescription. These individuals were 1.9 times as likely to require emergency hospitalization and had 2.9-fold higher all-cause mortality rates than those remaining on their medication during the period of observation.

Nichols and Brown (abstract 196) compared electronic medical and pharmacy records of 5,059 patients with type 2 diabetes with those of a control group. Depression was diagnosed in 18.5% and 11.4% of those studied. Depressed patients were younger and more often female, and their aggregate health care costs were 1.6 and 2.0 times higher than those of nondepressed patients with and without diabetes. The study found that 36.2% of depressed diabetic patients were on insulin, compared with only 24.5% of those who were not depressed.

Nilsson et al. (abstract 829) assessed sleep disturbances by questionnaire in 588 men and 253 women with type 2 diabetes, and in 21,867 men and 10,649 women without diabetes. Women with diabetes had a 54% increased risk of having "difficulties in falling asleep" and 42% increased risk of early awakening, with a 99% increase in use of hypnotic drugs, after adjustment for age and obesity. There was an association of sleep problems with increased mortality during 18-year follow-up in those with and without diabetes.

Mollema et al. (abstract 138) surveyed 1,484 members of the Dutch Diabetic Association and selected 119 patients with high scores on a Diabetes Fear of Injecting and Self-Testing Questionnaire. A total of 83 completed follow-up questionnaires. The results showed a high prevalence of psychological comorbidity, with 11% of those responding showing a high score on the Becks Depression Inventory, 13 and 11% having high anxiety and hostility scores on the Symptom Checklist −90, and 35% having agoraphobia.

Lernmark et al. (abstract 140) studied 67 children from the time of diagnosis of diabetes, finding a high correlation between anger and anxiety about injections with negative attitudes toward diabetes. Anger at the time of diagnosis was strongly associated with depression 5 years later. HbA_{1c} was not strongly predicted by psychological factors. Danne et al. (abstract 139) evaluated 2,077 adolescents from 17 countries, showing that HbA_{1c} was higher in ethnic minorities and that belonging to a minority group and having lower social status were associated with lower quality-of-life scores.

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