Cardiovascular Disease, Neuropathy, and Retinopathy

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This is the sixth of a series of six articles based on presentations at the American Diabetes Association Scientific Sessions held 6–10 June 2008 in San Francisco, California.

Role of glycemia in cardiovascular disease

Jacqueline Dekker (Amsterdam, the Netherlands) discussed the association between hyperglycemia and cardiovascular disease (CVD), particularly addressing A1C measurement in nondiabetic individuals. A1C, she noted, is considered a gold-standard measure of chronic glycemia in diabetic patients. In nondiabetic populations, its implications are somewhat less clear. In a study of 648 apparently healthy individuals, 12% had an elevated total A_1 level (measured in that study) not explained by measurement error or glucose intolerance and remaining in the same range over 3.5 years in 90% of those initially with high and in 68% of those initially with low baseline levels (1). There was no correlation with glucose tolerance, with caloric intake, or with physical activity, but A_1 level was associated with cigarette use and with clinically overt atherosclerosis, leading Dekker to conclude that "factors unrelated to glucose metabolism are the main determinants of A_1" in nondiabetic individuals, perhaps with bearing on risk of what are considered complications of diabetes. A subsequent study of 3,240 nondiabetic individuals showed weak correlation of A1C with fasting and 2-h glucose, cholesterol, and insulin. Weak but significant correlations were also found with erythrocyte characteristics, and cigarette use was associated with higher A1C, again suggesting nonglycemic effects on hemoglobin glycation (2). In the Islington Diabetes Survey, 1,084 participants had glucose tolerance tests and four different A1C assays. The 2-h postload glucose explained 19–41% of the variation in A1C, depending on the assay, and 26–48% of the variation was explained by the fasting glucose, with low and high glycators remaining constant over 4 years (3). If 50–80% is not explained by glycemia, the implication is, again, that although important in understanding diabetes, A1C must be considered cautiously with regard to implications of mechanistic causes of complications of hyperglycemia.

In a study of five individuals with low and seven with high A1C, relative to the 2-h glucose, there was a stronger relationship between glycated albumin and blood glucose and no differences in insulin, urea, free fatty acids, vitamin C, or intraerythrocyte organic phosphate. Higher erythrocyte 2,3 diphosphoglycerate levels and higher intracellular pH were found in the higher glycators (4). Dekker showed further evidence from a study of identical twins that A1C levels are genetically determined even in type 1 diabetes, explaining 62% of the variation in A1C (5). Potential glucose-independent mechanisms include hemoglobin glycation, erythrocyte cell membrane permeability to glucose, erythrocyte survival, and intraerythrocyte pH. In the Diabetes Prevention Program, among individuals with impaired glucose tolerance there were ethnic group differences in A1C not explained by glycemic differences, with blacks having mean A1C levels 0.5% greater than whites without a difference in glucose tolerance (6).

The relationship between hyperglycemia and mortality was best shown in the European DECODE study, with a stepwise relationship between 2-h glucose and mortality from low levels to impaired glucose tolerance to type 2 diabetes, with the association less convincing for fasting glucose (7). A meta-analysis of studies measuring fasting and 2-h glucose and A1C suggested that risk was related to all indicators, with a stronger relationship for women than for men; after adjustment for cardiovascular risk factors, the highest glycemia group had 19% greater risk than the lowest (8). In the Rancho Bernardo study, A1C was a better CVD predictor than fasting or 2-h glucose (9); in the Framingham Offspring study CVD risk increased 15% per SD increase in A1C, independent of fasting glucose and 2-h glucose (10); in the Epic-Norfolk study, there was a 1.2- to 1.3-fold increase in cardiovascular risk for each 1% increase in A1C (11); and in the Atherosclerosis Risk in Communities study, A1C was associated with both stroke and coronary heart disease risk (12). However, in the Women's Health Study myocardial infarction, stroke, and revascularization were not associated with A1C after adjustment for risk factors (13).

In Dekker's studies in Hoorn in the Netherlands, baseline examination of 2,848 men and women (aged 50–75 years) between 1989 and 1990 included glucose tolerance testing, with the correlation coefficients of A1C vs. fasting and 2-h glucose 0.24 and 0.14, respectively, in individuals with normal glucose tolerance, with 16% of this group having A1C >6%. Among 1,675 nondiabetic individuals with A1C measurement, 10 year follow-up showed strong associations of A1C both with fatal and with nonfatal CVD, with 1.7- and 3.0-fold increases in risk per 1% increase in A1C among men and women, respectively, while neither fasting nor 2-h glucose showed significant effect when other CVD risk factors were taken into account, leading Dekker to speculate that the continuous relationship between A1C and CVD is only to a limited extent due to glycemia. A1C might rather reflect an individual's vulnerability to hyperglycemia. She suggested that glucose tolerance testing remains important to determine an individual's status, with lifestyle intervention particularly effective among individuals with higher diabetes risk (14). She noted further that glucose is a direct measure of diabetes, while A1C is indirect and the time course of the relationship between increase in A1C and glycemia is not known. Furthermore, there is no information as to effectiveness of interventions

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in individuals with high A1C and normal glucose.

Hertzel Gerstein (Hamilton, ON, Canada) discussed the relationship between A1C and CVD in individuals with diabetes. The question of the consequences of diabetes should be considered to include eye (cataract, retina), kidney, nerve, peripheral arterial disease, ulcer/amputation, ischemic heart disease, stroke, cirrhosis, early death, cognitive decline, depression, hip fracture, imbalance and frailty, joint abnormality, erectile dysfunction, sexual dysfunction, and infertility. Not all of these abnormalities, he pointed out, are related to elevated glucose.

There is certainly a strong relationship between diabetes and CVD. A 2006 meta-analysis of 37 prospective studies from 1966 to 2005 including 447,064 diabetic patients (45% of whom were women) found that diabetic men and women were 2.0 and 3.1 times more likely to have CVD, respectively, after adjustment for other risk factors (15). In a population-based study from Ontario analyzing 379,003 diabetic and 9,018,082 nondiabetic individuals followed from 1994 to 2000, those with diabetes and those with history of myocardial infarction each had doubling of mortality risk; diabetic individuals developed high risk of CVD, as defined either by an annual event rate of 2% or an event rate equivalent to that associated with previous myocardial infarction, at an age ~15 years younger than that for nondiabetic individuals, whereas diabetic men and women entered the high-risk category at ages 41–48 and 48–54 years, respectively. Below age 40 years, diabetic individuals typically did not have a high risk by these definitions (16), but one may clearly consider diabetes "a serious disease."

A1C level does provide additional information pertaining to risk of complications of diabetes. In the UK Prospective Diabetes Study (UKPDS), for every 1% increase in A1C there was 21% higher mortality, 14% higher fatal/nonfatal myocardial infarction, 37% higher eye and kidney end points, 43% higher amputation, and 16% higher heart failure. A meta-analysis of prospective epidemiologic studies including the UKPDS, adjusting for age, smoking, glucose, and duration, showed 18% higher CVD levels for every 1% increase in A1C (17). Interestingly, however, there may be a less steep relationship between A1C and risk diabetic patients than with in those without diabetes (18). Why, Gerstein asked, is there a link between A1C and CVD? There is clearly a relationship between glucose and A1C in the general population, with potential for a direct adverse effect of high glucose per se. Alternatively, it may be that higher levels of glucose are associated with lower levels of insulin secretion or of insulin action, which might cause CVD—or there may be genetic or environmental factors that predispose to both dysglycemia and CVD (19). A final and very important question is whether A1C lowering reduces CVD. Gerstein reviewed data from the UKPDS with a 0.9% median difference in A1C over 10 years associated with reduction in microvascular disease and stated that only with metformin was there significant evidence of decreased macrovascular disease, despite its lesser effect in lowering A1C, suggesting that the method by which glucose is lowered might be important. (Subsequent to the lecture, the UKPDS group published 10-year follow-up data, however, showing that the glycemic intervention did lead to significant reduction in myocardial infarction or mortality (20). Gerstein concluded that "lowering A1C with some therapies in some people may reduce CVD," but cautioned that "we have to take the data" of the new studies to modify our understanding and our treatment recommendations. It may be that earlier treatment will be better and that "it is much easier to halt the process" than to reverse existing disease.

Vivian Fonseca (New Orleans, LA) discussed the "myth that insulin treatment is atherogenic," stating, rather, that endogenous hyperinsulinemia and the need for higher doses of exogenous insulin should be considered markers of underlying insulin resistance, which is the cause of greater levels of atherosclerosis. Certainly, the Diabetes Control and Complications Trial (DCCT) follow-up of the intensively treated group showed reduction in carotid atherosclerosis (21) and fewer cardiovascular events (22). In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, diabetic individuals entering the hospital with myocardial infarction benefited from insulin treatment (23), but neither the DIGAMI 2 study, in which the standard group had glycemia similar to that in the intervention group (24), nor the CREATE-ECLA study, in which a 25% glucose infusion was given with insulin and potassium (with the protocol failing to control glycemia [25]), improved outcome. Hyperglycemia was, however, a marker of adverse outcome in the latter study (26). Surgical intensive care unit patients show reduction in in-hospital mortality, but the data are more controversial in medical intensive care units. In the CLARITY-TIMI-28 study, both high and low admission glucose were associated with adverse outcome (27), Fonseca pointed out, emphasizing that "this is a very important issue . . . because you are likely to get hypoglycemia" with efforts to intensively treat diabetes. Indeed, he reviewed his studies showing increased risk of ischemic events during hypoglycemia or with rapid fall from glucose levels >100 mg/dl. Hypoglycemia, Fonseca stated, "confounds the whole business of delivering insulin to people with CVD."

CVD and diabetes

A number of studies presented at the ADA Scientific Sessions gave further information pertaining to CVD. Nishimura et al. (abstract 163) randomized 374 type 2 diabetic patients to insulin aspart versus regular insulin before meals, with 40–42% of patients also requiring an intermediate-acting or long-acting insulin. After a median of 4.5 years of follow-up, the cumulative cardiovascular event rate was 6 vs. 11%, although CVD and overall mortality did not differ. Rana et al. (abstract 79) followed 21,240 nondiabetic participants in the EPIC-Norfolk study for 11.4 years, finding that, compared with individuals with triglyceride <150 and HDL cholesterol >50/40 mg/dl for women/men (controlling for LDL cholesterol and other variables), men with high triglyceride alone had a 19% increase in coronary heart disease (CHD) event rates, those with low HDL cholesterol alone had a 65% increase in risk, and those with both features had a 50% increase in risk. For women, high triglyceride was associated with a 43% increase in risk and low HDL with a 56% increase, although those with both abnormalities had a nonsignificant 32% increase in risk—presumably an adverse consequence of carrying out an excess number of statistical tests.

Yoo and Chung (abstract 608) conducted a treadmill exercise electrocardiogram test on 114 asymptomatic type 2 diabetic patients, with coronary angiography when electrocardiographic changes occurred during exercise. Of those with >2 vs. ≤2 risk factors, 32 of 78 vs. 6 of 36 had CHD. Family history of CHD was associated with a 9.2-fold increase and diabetes duration >10 years with a 3.3-fold

increase in CHD risk, so that clinical characteristics remain important determinants of disease, useful in determining which individuals should have extensive testing. Wackers et al. (abstract 169) reported 4.8-year outcome of a study randomizing 1,123 type 2 diabetic patients without CHD symptoms to screening with stress adenosine myocardial perfusion imaging or to observation; the group had reported that 22% of those screened had evidence of ischemia (28). Of those screened, 15 of 558 (2.7%) had events, while 16 of the 561 (2.9%) nonscreened patients had myocardial infarction or cardiac death—evidence against a policy of aggressive screening. Those with moderate/large defects on imaging and those with ischemic ECG changes had 13.2 and 6.7% event rates, respectively, and additional predictive factors were male sex, associated with a 3.1-fold increase; peripheral vascular disease, 3.3-fold; LDL cholesterol, 1.2-fold per 10 mg/dl increase; creatinine, 1.2-fold per 0.1 mg/dl increase; and abnormal heart rate response to standing, a marker of cardiac autonomic dysfunction, 3.3-fold.

Rolin et al. (abstract 954) used the Danish National Diabetes, Disease and Death registries to show that incidence of CHD decreased from 5.4 to 4.0 per 1,000 person-years among nondiabetic but from 38.4 to 21.7 person-years among diabetic patients from 1995 to 2005, such that CHD risk among diabetic patients decreased from 3.8- to 2.9-fold that in the nondiabetic age-matched population. Ahn et al. (abstract 168) measured heart rate variability from the expiration-to-inspiration ratio and responses to the Valsalva maneuver and to standing in 1,126 diabetic patients, finding 56% with evidence of cardiovascular autonomic neuropathy. 131 had stroke over 6–8 years of follow-up, with risk factors including age, diabetes duration, hypertension, elevated creatinine, microalbuminuria, and retinopathy. Cardiac autonomic neuropathy was independently associated with a 2.8-fold increase in stroke risk. Eeg-Olofsson et al. (abstract 903) analyzed the relationship between weight status and CVD in 10,896 Swedish type 2 diabetic patients followed for 6 years, finding that overweight or obesity were associated with 39, 44, and 41% increases in risk of CHD, stroke, and mortality, respectively, with somewhat higher rates after adjustment for age, sex, diabetes duration, and smoking. Arsenault et al. (abstract 904) followed 21,729 individuals for up to 11 years, with 2,191 developing CHD. Physical inactivity was associated with a 30% increase in CHD. Increased BMI and, to a greater extent, waist circumference were associated with ~50–100% increases in CHD, with the combination of physical inactivity and obesity by either measure associated with 3- to 11-fold increases in CHD.

Polak et al. (abstract 261) analyzed carotid intima-media thickness in the Epidemiology of Diabetes Interventions and Complications follow-up of the DCCT, finding that although the rate of progression in former intensively treated patients was lower from 1 to 6 years after the conclusion of the DCCT, there was no difference in rate of progression between the former control and intensive treatment groups from 6 to 12 years. Similarly, Albers et al. (abstract 236) reported on a 14-year post-DCCT follow-up of 908 type 1 diabetic patients in which an increase was found in the prevalence of neuropathy from 9 to 24% among those formerly receiving intensive and from 17 to 33% among those formerly receiving conventional insulin treatment; the reduction in magnitude of difference between the groups suggests resumption of neuropathy development after discontinuation of intensive treatment. Rutledge et al. (abstract 311) reported on a 11–12 year post-DCCT follow-up of albuminuria (≥40 mg/24 h) development that found cumulative incidence of 18 vs. 25% in the former intensive glycemic treatment group versus the control group, although analysis of the development pattern suggested that the protective benefit was limited to the first 7–8 years after the conclusion of the DCCT. The "metabolic memory" phenomenon of benefit from early intervention may then be of limited duration in type 1 diabetes.

Neuropathy

Kulzer et al. (abstract 1853) studied 211 diabetic patients and found neuropathy in 39%, of whom 48% had evidence of depression, which emerged as a frequent comorbid condition with painful neuropathy. Flottemesch et al. (abstract 361) followed 14,144 adult diabetic patients of whom 2,179 had a diagnosis of and/or were treated for depression, the latter group with lower rates of A1C and LDL cholesterol monitoring. Selvarajah et al. (abstract 1864) analyzed the effect of depression on the response of 28 diabetic individuals with painful neuropathy to sativex, a potential therapeutic agent, compared with placebo. No treatment effect was shown, but depressed patients improved significantly whether receiving active treatment or placebo, suggesting that this is an important confounder of clinical trials in painful diabetic neuropathy. Similarly, Echeverry et al. (abstract 115) treated 56 depressed diabetic patients with 50–100 mg sertraline daily versus placebo for 6 months and found significant improvement in A1C and in quality of life score both with and without pharmacologic antidepressant treatment, suggesting a benefit of the greater degree of health care provider interaction.

A number of newly discovered factors may play roles in the development of diabetic neuropathy. Pitocco et al. (abstract 157) studied a polymorphism in osteoprotegerin, an important regulator of bone remodeling, and found patients with Charcot neuroarthropathy to have a 2.4-fold greater likelihood of having the G allele and a 40% reduction in presence of the C allele, while there was no association with diabestic neuropathy alone. Carvalho et al. (abstract 242) studied animal wound healing models not expressing the neurokinin-1 receptor, the site of action of substance P, or treated with the receptor antagonist CJ 12,255, showing reduction in wound healing in nondiabetic animals but no effect in diabetic mice, suggesting this to be a potential area for pharmacologic treatment.

Chen et al. (abstract 1942) administered autologous bone marrow mesenchymal stem cells by multiple intramuscular and subcutaneous injections into lower limbs with an ankle-brachial index of <0.90 and found a reduction in rest pain of 40%, with a 140% increase in pain-free walking distance; control patients had a 10% reduction and 10% increase in the respective measures. Fifteen of 18 foot ulcers healed among those receiving transplants, but 9 of 20 ulcers healed among controls, indicating this could potentially be a useful approach. Kipnes et al. (abstract 235) administered vascular endothelial growth factor zinc finger protein activator SB-509 or placebo intramuscularly to 24 patients with diabetic neuropathy and found improvement in motor and sensory nerve conduction velocity and in vibration sensation at 6 months, suggesting potential nerve regeneration.

Jeffcoate et al. (abstract 158) performed a randomized controlled trial of three dressing products used at least twice weekly, a simple knitted viscose primary dressing (N-A), an antiseptic preparation (Inadine) and sodium carboxymethylcel-

lulose (Aquacel) in 317 diabetic patients with foot ulcers also receiving standard care with regular surveillance, sharp debridement, and appropriate off-loading. At 24 weeks, 39, 44, and 45% of the respective groups had healed, with the authors concluding that there was no difference in the effectiveness of the three dressings. Bowling et al. (abstract 1093) compared the Visitrak digital planimetry system to use of a paper tape measure to ascertain wound circumference; the latter was more accurate for wounds <2.5 cm^2 and considerably less expensive, with the two approaches otherwise quite similar, suggesting the "low tech" approach to be preferable. LeMaster et al. (abstract 160) randomized 79 patients with diabetic neuropathy to control or walking exercise groups, the latter using pedometers, and both groups were given diabetic foot care education, regular foot care, and eight sessions with a physical therapist. There was one plantar ulcer in each group at 6 months and five vs. one ulcer at 12 months, suggesting walking to be potentially beneficial in these patients. Game et al. (abstract 1094) screened 111 foot ulcers from 93 consecutive diabetic patients in 2007 and found methicillin-resistant *Staphylococcus aureus* in 15%, increased from 10% in 2002; that most of the patients lived in the community rather than being hospitalized and with prolonged use of broad-spectrum antibiotics also no longer a risk factor suggests that screening should be performed more widely for this organism.

Dellon et al. (abstract 1090) reported on a prospective (but neither randomized nor controlled) follow-up of 618 diabetic individuals with a positive Tinel sign over the tibial nerve in the tarsal tunnel and painful neuropathy symptoms undergoing decompression surgery, reporting that at 1-year follow-up among 146 of the patients, pain was reduced on average from 8.5 to 1.5 on a 10-point scale, with improvement in 2-point discrimination in somewhat under one-quarter of the population and foot ulceration in fewer than 1%. A controlled study would be required to ascertain whether the procedure is actually of benefit. Similarly, Kempf et al. (abstract 489) treated 167 patients with painful diabetic neuropathy with a high-frequency external muscle stimulation device, reporting reduction in a variety of symptoms, again without a control group to establish the validity of the response.

Ejskjaer et al. (abstract 298) administered the ghrelin agonist TZP-101 to 10 patients with severe diabetic gastroparesis, showing improved gastric emptying for liquids and solids, with meal-related symptom score improved in five of eight patients studied, on average by 24%, and with 37% reduction in postprandial fullness.

Retinopathy

Rosenstock et al. randomized 1,017 type 2 diabetic patients to glargine daily vs. NPH twice daily plus regular insulin as needed for 5 years, with baseline A1C 8.4 vs. 8.3% and a significant 0.2% greater reduction in A1C with NPH but trends to less weight gain and hypoglycemia with glargine. Diabetic retinopathy was present at baseline in 16 vs. 12%, with noninferiority of glargine, as 14 vs. 16% showed retinopathy progression by $\geq$3 steps after 5 years. Thomas et al. (abstract 809) found retinopathy using a nonmydriatic camera in 15% of 336 newly diagnosed type 2 diabetic patients, finding similar age, fasting glucose, A1C, and fasting and postprandial insulin but a 2-h postprandial glucose of 283 vs. 261 mg/dl in those with versus without retinopathy, respectively. Those with sight-threatening retinopathy or maculopathy had higher systolic blood pressure.

Sun et al. (abstract 816) studied type 1 diabetic individuals with disease duration $>$50 years, finding that of 46 with a mean 24 years of follow-up, those with greater progression of retinopathy had a higher 7-year mean A1C and the serum advanced glycation end product carboxyethyl-lysine. Of 287 studied at one time point, proliferative retinopathy again correlated with this measure, but not with A1C, and there was no association of retinopathy with elevations in carboxymethyl-lysine, furosine, or 2-aminoadipic acid. Wu et al. (abstract 54) analyzed retinal sections from nondiabetic individuals and from diabetic patients without retinopathy, with moderate nonproliferative retinopathy, or with proliferative diabetic retinopathy. Macrophages partially colocalized with apoliprotein B100 in sections of patients with proliferative retinopathy and with intraretinal oxidized LDL cholesterol in all three diabetic groups but not in the nondiabetic group, correlating with retinopathy severity. Glucose- and oxidative stress–modified LDL cholesterol might cause retinopathy, perhaps interfering with retinal capillary pericytes. Zhang et al. (abstract 50) reported that human retinal pericytes exposed to heavily oxidized glycated LDL cholesterol showed increased monocyte chemoattractant protein (MCP)-1 production, with the antiangiogenic pigment epithelium-derived factor (PEDF) reducing levels of the MCP-1 and peroxynitrite, reflecting an effect on oxidative stress. Wang et al. (abstract 715) from this group reported similar suppression of renal MCP-1 and other inflammatory factors with PEDF overexpression. Villacampa et al. (abstract 49) studied IGF-I transgenic diabetic mice, which develop features of nonproliferative retinopathy; overexpression of PEDF reduced retinal neovascularization and expression of inflammatory molecules.

Geraldes et al. (abstract 52) showed that exposure of isolated bovine retinal pericytes to high glucose increased pericyte apoptosis and reduced response to platelet-derived growth factor (PDGF) by a mechanism involving protein kinase Cδ and p38α mitogen-activated protein kinase, with models not expressing active forms of these enzymes showing resistance to pericyte loss with hyperglycemia and increased PDGF response, which might offer a mechanism of the long-term adverse effect of hyperglycemia. Obrosova et al. (abstract 51) found poly(ADP-ribose) polymerase (PARP) expression in the lens and retina. Cataract occurred in 94% of streptozotocin-diabetic rats but in 69 and 50% of diabetic animals administered two different PARP inhibitors, which also reduced retinal oxidative-nitrosative stress and glial activation. Behl et al. (abstract 48) found that rat microvascular endothelia cells incubated in high glucose had increased apoptosis, which decreased 60–70% by inhibiting transcription of the forkhead factor FOXO1 either with small interfering RNA for FOXO1 or by inhibiting tumor necrosis factor-α; translocation of FOXO1 to the nucleus was five times greater in retinal digests from animals with diabetes for 6 months. Retinal cell apoptosis and pericyte ghost formation, increased by diabetes, were reduced 75% with intravitreal FOXO1-specific siRNA. Roy et al. (abstract 47) gave three intravitreal injections of siRNA targeted to fibronectin, which is overexpressed in diabetic retina, over a 4.5 month period to streptozotocin-diabetic rats. Retinal fibronectin expression and retinal capillary basement membrane thickening were both reduced 1.5 months later.

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