Treatment Issues in Type 2 Diabetes

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This is the fourth in a series of reports on the American Diabetes Association (ADA) 61st Scientific Sessions held in Philadelphia, PA, in June 2001. It covers topics related to the treatment of type 2 diabetes.

Insulin resistance
Perriello et al. (263-OR) performed hyperinsulinemic clamps in five normal individuals from 5:00 to 8:00 A.M. and from 5:00 to 8:00 P.M., on both occasions after a 9-h fast (abstract numbers refer to the Abstracts of the 61st Annual Meeting of the American Diabetes Association, Diabetes 50 [Suppl. 2]:1–A649). Insulin action decreased 27% in the evening, partially explaining the decrease in glucose tolerance in the afternoon versus early morning hours. Zaccaro et al. (301-PP) compared insulin sensitivity calculated from the frequently sampled intravenous glucose tolerance test with surrogate measures based on fasting insulin and glucose levels in 1,118 persons in the family members in the Insulin Resistance Atherosclerosis Study (IRAS), showing a greater degree of genetic contribution to specifically measured insulin sensitivity than to the measurement of fasting insulin alone, the product of fasting insulin and fasting glucose divided by 22.5 (the “homeostasis model” [HOMA] measure), or the reciprocal of the product of fasting insulin and glucose (the “Bennet index”). These surrogate measures of insulin sensitivity may therefore be less useful than previously thought. Mather et al. (9-LB) reported that the T786C variant of the endothelial isoform of nitric oxide synthase was associated with insulin resistance, perhaps contributing to its association with endothelial dysfunction. Meyer et al. (198-OR) compared hepatic and renal glucose production, which were 10.3 and 3.6 μmol·kg⁻¹·min⁻¹, respectively, in 10 type 2 diabetic patients and 8.4 and 2.16 μmol·kg⁻¹·min⁻¹ in 12 nondiabetic control subjects, using triated glucose turnover and renal vein glucose measurement. During hyperinsulinemic-euglycemic clamps, hepatic and renal glucose production decreased 30 and 33% in the diabetic patients and 52 and 62%, respectively, in the control subjects, suggesting substantial renal contribution to glycemia in type 2 diabetes. Woerle et al. (413-P) used similar techniques following overnight insulin infusion in 30 patients with type 2 diabetes compared with 26 control subjects, showing somewhat greater suppression of hepatic than renal glucose release in the patients.

In a clinical study, Cagliero et al. (362-P) reported that insulin sensitivities were reduced by 78 and 62%, respectively, in 10 and 12 patients treated with the atypical antipsychotic agents clozapine and olanzapine, in comparison with insulin sensitivity in patients treated with risperidone, suggesting that the former agents may induce insulin resistance. Spoelstra et al. (875-P) used a pharmacy dispensing record system with ~320,000 patient histories, including 3,104 newly diagnosed patients with type 2 diabetes. Of this group, 15.4% of those treated with an atypical antipsychotic drug required insulin within 3 months after initiation of oral agent treatment, but 7.5% of the remaining patients required insulin after an initial period of oral hypoglycemic treatment. Bell et al. (819-P) examined the association between cigarette smoking and 5-year incidence of diabetes in the IRAS in 906 subjects without pre-existing diabetes at baseline. At the 5-year follow-up, cigarette smokers were 2.8 times more likely to develop diabetes after adjustment for ethnicity, baseline glucose tolerance, age, sex, cardiovascular disease risk factors, BMI, waist circumference, and behavioral risk factors.

AMP-activated protein kinase
At a seminar on new therapeutic targets for type 2 diabetes, Lee Witters, Dartmouth, NH, described AMP-activated protein kinase (AMPK) as “a metabolic sensor-effector,” with metabolic stress increasing the AMP/ATP ratio, activating AMPK, and thereby leading to increased nitric oxide synthase, greater GLUT4-mediated glucose transport, and many other effects. AMPK has subunits α, β, and γ1, -2, and -3, with a complex molecular structure. The γ subunit plays a role in AMP sensitivity, and mutations that have been described to date are associated with increased enzyme activity in the absence of AMP, leading to increased muscle glycogen and to a form of Wolff-Parkinson-White syndrome.

The AMPK activator 5-aminooimidazole-4-carboxamide 1-β-p-ribonurano side (AICAR) is thought to increase muscle glucose uptake by mimicking the effect of exercise-related muscle contraction, an action independent of and complementary to the effect of insulin. Young et al. (243-OR) described a number of effects of a 7-day course of AICAR on rat skeletal muscle gene expression, including neuronal nitric oxide synthase and citrate synthase without increase in GLUT4 mRNA, mimicking exercise training-induced alterations. Coven et al. (245-OR) found that AMPK is activated to a similar extent in heart as in skeletal muscle during exercise, suggesting an important role in regulating myocardial metabolism. Aschenbach et al. (244-OR) reported that AICAR decreased blood glucose 50 mg/dl in normal rats over a 120-min period, increased the α2 but not the α1 isoform of AMPK, and increased muscle glycogen levels, although glycogen synthase increased in red muscle and decreased in white muscle. Nakano et al. (917-P) also showed AICAR selectively activated α2 AMPK with an acute increase in glucose transport, and showed that administration three times daily for 4–7 days increased GLUT4 protein 2.5-fold in mouse skeletal muscle. Richter et al. (249-OR) studied six normal men during
exercise preceded by high versus low carbohydrate intake. Muscle biopsies at 0, 10, and 60 min of exercise showed glyco-
gen concentrations of 843, 697, and 378 vs. 198, 162, and 121 μmol/g, respecti-
vely, with leg glucose clearance during exercise twice as great in the glycogen-depleted state. α2-AMPK activity in-
creased 1.6-fold with exercise in the glycogen depletion group only. α1-
AMPK did not change with exercise in ei-
 ther group.

AMPK may play a role in the treat-
ment of diabetes. Kraegen et al. (324-PP) showed that a single injection of AICAR increased muscle glucose uptake and gly-
gen concentration during a hyperinsuline-
mic-euglycemic clamp over the sub-
sequent 2 h and also increased insulin sup-
pressibility of hepatic glucose produc-
tion, suggesting a potential approach for pharma-
cologic therapy. Islam et al. (1318-P) treated insulin-deficient strep-
tozotocin-induced diabetic rats with AICAR, which decreased glucose from 501 to 170 mg/dl at 4 h, with a 2.6-fold lower area under an oral glucose tolerance curve after 4 days. It appears that changes in AMPK activity occur with administra-
tion of metformin. Musi et al. (1127-P) found 2.7- and 1.5-fold increases, respec-
tively, in α1 and α2 AMPK activity in rat epidermoleans muscle incubated for 3 h with metformin; these increases were asso-
ciated with a 40% increase in glucose uptake, with an additive effect of insulin. A 5-day oral course of metformin also in-
 creased activity of both AMPK isoforms, but did not change AMPK protein con-
tent. Zhou et al. (1128-P) showed a three-
fold increase in hepatocyte AMPK activity after incubation with metformin or with AICAR, with inhibition of acetyl-CoA car-
boxylase, induction of fatty acid oxida-
tion, and suppression of mRNAs for lipogenesis.

Insulin sensitizers
Fleming et al. (448-P) reported a study of 165 sulfonylurea-treated patients given n-
dehio-insulin, a precursor of the mediator released by hydrolysis of a membrane-
bound mostolphosphoglycan when in-
sulin binds to its receptor. In comparison with placebo, over 3 months HbA1c fell 0.16% versus increasing 0.2%. The differ-
ence was most pronounced among pa-
tients with fasting glucose <180 mg/dl whose HbA1c fell 0.52% while increasing 0.27% with placebo. Improvement of glu-
cose with either sulfonylureas or met-
formin may directly improve macrovascular risk factors. Celalu et al. (601-P) treated 81 type 2 diabetic patients for 6 weeks, showing that plasminogen activator inhibitor type-1 decreased from 202 to 166 ng/ml with glipizide GITS and from 201 to 174 ng/ml with metformin. Mugellini et al. (582-P) studied 164 non-
smoking patients with type 2 diabetes who were not receiving hypolipidemic drugs, diuretics, β-blockers, or thyr-
oxine; had normal renal function; and were treated with glimepiride versus met-
formin. With similar blood glucose lowering, there was no difference in the effects of the two drugs on lipoprotein(a) [Lp(a)]. HbA1c decreased from 8.5 to 6.9% vs. 8.4 to 7.0%, and Lp(a) decreased from 45 to 39 mg/dl and from 48 to 43 mg/dl, respectively.

**Peroxisome proliferator–activated receptor–γ mechanisms**
Yamauchi et al. (1578-P) pointed out that high-fat diet–induced insulin resistance is blocked by activation of peroxisome pro-
liferator–activated receptor (PPAR)-γ, thiazolidinediones (TZDs), and by mod-
erate reduction of PPAR-γ activity by het-
ebrozygic deficiency in mice and PPAR-γ polymorphism with lower tran-
scriptional activity in humans. Lipoatro-
phy, however, with severe reduction in PPAR-γ activity, is associated with insulin resistance. PPAR-γ may regulate fuel partition-
ing among tissues, and there may be an “optimal” level of PPAR-γ activity for insulin sensitivity without development of obesity. A number of studies examined effects of PPAR-γ deficiency or excess in specific tissues. Chen et al. (230-OR) showed that, when fed a high-fat diet, mice with muscle PPAR-γ deficiency have higher serum insulin levels and develop more severe glucose intolerance than controls, but that rosiglitazone (RGZ) im-
proved glucose tolerance and decreased circulating insulin levels in a fashion sim-
ilar to that without the gene defect. Thus, muscle PPAR-γ does not appear to play a major role in basal insulin sensitivity or in the response of mice to TZD treatment. Rosen et al. (208-OR) showed a normal metabolic phenotype in mice with tar-
ged ablation of PPAR-γ in β-cells with or without a high-fat diet. Takasawa et al. (27-LB) had previously shown that mice that did not express PPAR-γ were pro-
tected from an increase in white adipose tissue mass and developed less insulin re-
sistance on a high-fat diet. Using trans-
genic mice overexpressing the constitu-
atively-active Ser112Ala mutation of PPAR-γ2 in white and brown adipose tissues, they found greater weight gain and increase in epididymal fat mass on a high-fat diet, with a 2.1-fold increase in fasting insulin and evidence of insulin resis-
tance, suggesting an adverse effect of PPAR-γ2 activation. Hefener et al. (1005-P) studied mice heterozygous for a PPAR-γ gene deletion and for an insulin receptor gene deletion. The insulin resis-
tance, hyperglycemia, hyperinsulinemia, high free fatty acid (FFA), and decreased adipocyte cell size seen with the heterozy-
gous insulin receptor gene deletion alone were reversed with the addition of PPAR-γ gene deletion. Miles et al. (1695-P) showed that PPAR-γ gene dele-
tion heterozygous mice had a lessened ef-
fector of aging on insulin sensitivity. They did show insulin resistance and an in-
crease in fat mass when given a high-fat diet; both of these abnormalities showed improvement with the administration of troglitazone (TGZ).

**TZDs**
Buchanan et al. (327-PP) presented fol-
low-up data from the Troglitazone in Pre-
vention of Diabetes (TRIPOD) study of 235 women who had had gestational di-
abetes randomized to placebo or TGZ. Annual incidence rates of type 2 diabetes during the 30-month study were 12.3 and 5.4%, respectively. Analysis of treated pa-
tients showed that the 35 subjects whose insulin sensitivity did not improve had an annual diabetes incidence of 9.8%, and that the 42 subjects whose insulin re-
sponse to intravenous glucose declined only slightly had a 5.8% annual inci-
dence, while none of the 31 subjects who showed a large improvement in insulin sensitivity developed diabetes during the follow-up period. During the first 8 months after stopping treatment, 6 of 40 who had received placebo developed di-
betes, while only 1 of 41 treated with TGZ had such an effect, suggesting that not only was there not a “catch-up” of patients off treatment, but that there actually ap-
ppeared to be benefit lasting well beyond the treatment period.

Banerji et al. (356-P) measured total body fat and lean body mass by dual-
energy X-ray absorptiometry and total ab-
dominal visceral and subcutaneous (SC)
Prospects on the News

Lipid effects of TZDs
At a symposium at the ADA meeting sponsored by the Academy for Healthcare Education, Peter Tontonoz, Los Angeles, CA, discussed the PPAR family of nuclear receptors, which differ from most nuclear receptors in having broad ligand specificities, showing activation by physiologic concentrations of a range of native and modified polyunsaturated fatty acids (1). PPAR-α, expressed predominantly in the liver, controls fatty acid oxidation, with the fibrates hypolipidemic drugs acting at this site. PPAR-γ is expressed in a number of tissues involved in lipid uptake and storage rather than catabolism. In addition to acting in adipocytes, PPAR-γ is expressed in mammary and colonic epithelium and in macrophages (2) and in development in placenta and in the heart (3). Although PPAR-δ is more widely expressed than the other PPARs and also plays a role in lipid metabolism, its role in physiology and disease is not yet as well understood (4).

Steven A Kliever, Research Triangle Park, NC, discussed the results of differential gene expression studies assessing the actions of PPAR-γ. Insulin-resistant Zucker diabetic fatty rats showed a decrease in free fatty acid levels 6 h after administration of a PPAR-γ agonist, while the fall in glucose and triglyceride levels with this agent were not seen until several days of treatment. Using a global mRNA identification system, ~10% of white adipose tissue genes showed at least a 50% change in expression, with upregulation of glycolgen synthase and all genes involved in lipogenesis, while in liver ~2% of genes showed such a change, predominately with decreases in expression of genes involved in gluconeogenesis. In muscle, only 1% of genes showed a change of at least 50%, with the major effects being a decrease in fatty acid transport genes and a decrease in expression of pyruvate dehydrogenase (PDH) kinase 4, which is responsible for inactivation of PDH. Thus, the overall effect is to increase glucose metabolism. Kliever suggested these findings to be consistent with the main effect of PPAR-γ being on adipose tissue, with consequent flux of fatty acids away from liver and muscle, causing increased muscle glucose oxidation via the increase in PDH and decrease in hepatic gluconeogenesis.

Harold Lebovitz, Brooklyn, NY, further discussed PPAR-γ agonists, explaining that they have a major action in adipose tissue. PPAR-γ agonists cause differentiation of stem cells into adipocytes and decrease adipocyte release of FFAs and cytokines, such as TNF-α, all of which appear to play roles in the development of insulin resistance. Circulating FFAs interfere with the insulin action cascade, thus blocking glucose transport; a major site of action involves the phosphorylation of insulin receptor substrates 1 and 2. In human studies, RGZ 4 mg twice daily lowers FFA levels by 25%. Lebovitz showed that RGZ decreases triglyceride levels, particularly in patients who are initially hypertriglyceridemic, and increases HDL2 levels by ~15%. Moreover, although it increases LDL levels, RGZ also increases particle size, suggesting decreased atherogenicity. New agents with mixed PPAR-α and -γ agonist action cause even greater 43% decreases in triglyceride and 15% increases in HDL levels. Noting that there is evidence that inflammation plays a role in atherosclerosis, it is of interest that RGZ is associated with a 40% decrease in C-reactive protein in some studies. Insulin resistance is associated with vasoconstriction, perhaps reflecting a decrease in the vasodilatory effect of insulin in increasing nitric oxide synthase. Studies with TGZ have shown restoration of endothelial function, and RGZ is associated with a 2- to 4-mmHg fall in blood pressure levels. In vitro, RGZ decreases coronary artery smooth muscle cell proliferation, and human studies of TGZ have shown a decrease in carotid intima-media thickness. RGZ may also decrease the hypercoagulable effect of insulin resistance, with evidence of a decrease in the elevated levels of plasminogen activator inhibitor 1.

An important question concerns whether PPAR-γ agonists decrease the loss of β-cell function characteristic of type 2 diabetes. Thirty-month open-label studies with RGZ suggest maintenance of glycemic benefit, although one may argue that in such studies the patients who decline further participation are those who do not respond to treatment, leading one to incorrectly infer that ongoing benefit is achieved. RGZ does, however, decrease insulin levels and increase insulin sensitivity with some evidence of improvement in β-cell function, and in animal studies, there is evidence of β-cell preservation with RGZ but not with glyburide or metformin.

Barbara C. Hansen, Baltimore, MD, discussed the effect of the PPAR-δ agonist GW501516, an agent designed by study of the PPAR-δ structure using combinatorial chemistry. In vitro, GW501516 increased expression of the reverse cholesterol transporter, ATP-binding cassette A1, and increased apoA1-specific cholesterol efflux. In the nonhuman primate model of rhesus monkeys with central obesity, hypertriglyceridemia, hypertension, low HDL cholesterol, a range from normal to impaired glucose tolerance, without diabetes and with fasting insulin levels approximately fivefold increased, the agent led to a dose-dependent near-doubling of HDL cholesterol (from baseline levels in this species ~60 mg/dl), a 50% decline in triglyceride levels, and a 20% fall in LDL cholesterol, with lowering of small dense LDL levels. There was also a decrease in insulin levels, suggesting improvement in insulin sensi-
tivity. Body weight did not increase. Hansen suggested that the agent may enhance reverse cholesterol transport and may play a role in lipid treatment in individuals with diabetes.

Four studies of patients previously treated with TGZ were displayed at the ADA Annual Meeting. Davidson et al. (437-P) randomized 39 patients to PGZ 45 mg versus RGZ 8 mg; Geggick and Althermer (452-P) randomized 125 patients to PGZ (81% receiving 45 mg) versus RGZ (77% receiving 8 mg); Khan et al. (477-P) randomized 97 patients to PGZ versus RGZ in doses proportionate to their initial TGZ dose; and King and Armstrong (482-P) randomized 61 patients to PGZ 45 mg versus RGZ 8 mg. HbA1c fell from 7.5 to 7.1% with PGZ, whereas it did not change with RGZ in the Davidson et al. study, although it was similar in the three larger studies. Davidson et al. found that HDL cholesterol increased from 47 to 54 mg/dl and from 40 to 47 mg/dl, respectively, with the two agents. Geggick and Althermer found that the triglyceride:HDRL ratio decreased from 5.7 to 4.7 mg/dl with PGZ and increased from 4.7 to 7.0 mg/dl with RGZ. Khan et al. reported increases in HDL from 42 to 45 mg/dl with both agents, and a fall in LDL from 120 to 101 mg/dl and in triglyceride from 191 to 176 mg/dl with PGZ, as compared with no change with RGZ. King and Armstrong noted that HDL increased 12% with PGZ and decreased 5% with RGZ, but administration of the latter was initiated with a higher HDL level. Although meta-analysis of the combined group of 322 patients would be of interest, there appears overall to have been no difference in HbA1c, an increase in HDL cholesterol with both, and no consistent difference in LDL cholesterol. Two of the studies suggest greater triglyceride-lowering with PGZ. Brunzell et al. (567-P) reported an 8% increase in LDL cholesterol over 8 weeks and stabilization for the next 16 weeks with RGZ 4 mg twice daily, but with a decrease in LDL density and an improvement in HDL cholesterol via selective increases in HDL2.

Nonmetabolic effects of PPAR-γ and TZDs
Zheng et al. (297-PP) cultured mouse mesangial cells with or without TGZ. PPAR-γ was present in the cells, although at lower levels when isolated from animals with diabetes and with exposure to glucose levels of 25 mmol/l rather than 6 mmol/l. TGZ decreased TGF-β mediated type I collagen synthesis, reversing the increase in collagen synthesis seen with exposure in vivo or in vitro to high glucose. Matsumura et al. (294-PP) showed that in cell culture systems, increased medium glucose led to increased mitochondrial superoxide generation, in turn decreasing PPAR-γ2 activation by decreasing its serine phosphorylation, suggesting a link between hyperglycemia, oxidant stress, and insulin resistance. Sidell et al. (277-OR) treated obese or lean Zucker rats with RGZ versus buffer, and then perfused the hearts ex vivo under ischemic conditions, with tritiated glucose to measure glucose utilization and 31P nuclear magnetic resonance to follow intramyocardial pH and energetics. At reperfusion, the control obese Zucker hearts showed recovery of 52% of initial contractile function, while those treated with RGZ showed 81% recovery, with the decrease in glucose uptake during ischemia normalized by RGZ treatment. Intracellular ATP and pH after ischemia were lower in the control than the RGZ-treated hearts. PPAR-γ agonists may have direct or indirect cardioprotective properties when administered before an episode of ischemia.

Diabetes in the elderly
Reuben Andres, Baltimore, MD, discussed the question of whether diagnostic standards for diabetes should be age-specific, pointing out that the ADA received “considerable flack” for its 1997 recommendation that fasting glucose is sufficient for diabetes and that the glucose tolerance test need not be used. The concept of glucose tolerance was originally based on the development of glycosuria after oral glucose, so that with their higher renal threshold, older individuals would be expected to show “better” glucose tolerance. Oster reported diabetes as infrequent when studied in 1892. Assessment of the blood glucose response to oral glucose began around 1920, with evidence of worsening glycemic response with age in almost all analyses. This may be due to disease, medicines, physical activity, physical conditioning, or change in body composition, but even while taking these into account, age is significantly associated with the response to a glucose load. The Baltimore Longitudinal study, which began in 1962, has shown that glucose tolerance declines with age, with particular worsening of the 2-h glucose rather than the fasting glucose, so that “if you try to come up with one number” for use of fasting rather than 2-h glucose, “it would be meaningless” with increasing age. According to National Health and Nutrition Evaluation Study (NHANES) and Rancho Bernardo data, as well as glucose tolerance results from the Baltimore study, that compared fasting and 2-h glucose levels in ~6,000 persons, younger individuals showed closer agreement between fasting glucose over 126 mg/dl and 2-h glucose over 200 mg/dl, while older individuals were likely to have high 2-h levels without elevated fasting glucose levels. This can also be seen with impaired glucose tolerance, with the 140 and 110 mg/dl cutoffs for 2-h and fasting glucose, respectively, similarly showing substantial agreement only for younger persons. Sequential data shows that the time from abnormal 2-h to abnormal fasting glucose, either for impaired glucose tolerance or for frank diabetes, is ~8 years. Andres suggested that, particularly among older individuals, use of fasting glucose alone leads to undue delay in diagnosis of diabetes.

Wilfred Fujimoto discussed the pathophysiology of diabetes in older individuals, with both insulin resistance and abnormal β-cell function. Initially, in response to insulin resistance, there is an increase in insulin secretion, with subsequent failure of the compensation leading to glucose intolerance and finally to hyperglycemia of sufficient severity to diagnose diabetes. There may be altered stimulus secretion coupling of glucose as a secretagogue, or there may be altered processing, e.g., of proinsulin to insulin. Older persons have lessened peripheral sensitivity to insulin, while showing similar sensitivity of hepatic glucose production to the suppressive effect of insulin. Increased age is associated with decreased glucose tolerance with greater incremental insulin response, with euglycemic clamp data showing decreased insulin sensitivity. Younger individuals also show increased muscle blood flow in response to hyperglycemia, but this is not seen in older persons, suggesting resistance to the vasodilatory effect of insulin with age. With a 100-g oral glucose tolerance test over 270 min, older individuals show higher blood glucose, with a delay in the rise in arterial insulin levels, suggesting a component of insulin deficiency. Other
studies comparing weight- and fasting insulin- and glucose-matched older and younger individuals show somewhat higher 2-h glucose levels in the former and decreased glucose disappearance in response to insulin, suggesting insulin resistance. The effect of glucose to potentiate the insulin response to the nonglucose secretagogue arginine also decreases with age. Several studies have shown abnormal processing of proinsulin to insulin. Comparing older and younger individuals with similar glucose tolerance, proinsulin levels are higher at baseline and during glucose tolerance test in older persons, and the proinsulin-to-insulin ratio increased, suggesting decreased conversion. In studies of Japanese Americans, those who develop diabetes have β-cell dysfunction and impaired glucose tolerance, but not decreased physical activity or increased abdominal fat.

Edward Gregg, Atlanta, GA, discussed the relationship between diabetes complications and aging as well as potential preventative approaches. Diabetes was present in 19% of those aged 60 years and older in NHANES III. Census data indicate increasing prevalence of older persons in the overall population, so that the steepest increase in diabetes in the U.S. will be in individuals over age 65 years, who now comprise 40% of patients with diabetes, but will account for 65% in several decades. Cognitive impairment, physical disability, impaired social function, and impaired psychological function should all be considered potential adverse effects of diabetes. Cognitive impairment develops in one-third of women and one-sixth of men over age 55 years and may be increased with diabetes, perhaps because of hyperglycemia, hypoglycemia, polyparathyroidism, the need for repeated surgery, vascular disease, or a common genetic predisposing factor for both diabetes and dementia. In the Study of Osteoporotic Fractures, diabetes status was associated with worse cognitive function among women and with a 60% greater risk of a major decline in cognitive function, with increasing duration of diabetes particularly associated with cognitive decline (5).

There are five additional studies that have addressed this question; four have confirmed this relationship between diabetes and cognitive decline. Addressing clinically diagnosed dementia, the Rotterdam Study (6) of 6,000 adults showed a doubled prevalence of dementia among individuals with diabetes, with a fourfold increase in patients treated with insulin, which presumably is a marker of diabetes severity.

Physical disability is an important factor in quality of life, affecting 20% of the older population. NHANES III data show that inability of women aged 65 years and older to perform a variety of physical tasks was more than doubled with diabetes. Among individuals with and without diabetes without physical disability at baseline, those with diabetes have a twofold likelihood of developing physical disability, in part because of retinopathy and neuropathy. Women with diabetes have a higher risk of falling, presumably due to impaired physical function, so that although their bone density is higher, they have a greater risk of hip fracture than individuals without diabetes. Diabetes is also associated with psychiatric illness, with 11% of patients having major depression. Gregg noted that improving glycemic, lipid, or blood pressure control may not improve cognition. The Systolic Hypertension in Europe Trial showed decreased dementia with blood pressure treatment (7). Intervention to improve physical disability and other quality of life outcomes has not been studied, although there is evidence that healthy lifestyle leads to a lag in the onset of disability.

Jeffrey Halter, Ann Arbor, MI, discussed the challenge of treating diabetes in older people, with 20–25% of the older population having diabetes. Risks of adverse micro- and macrovascular outcome increase with increasing degrees of hyperglycemia, with 2-h postchallenge hyperglycemia particularly associated with adverse outcomes. He pointed out that the typical individual aged 65 and 75 years has an average remaining life expectancy of 18 and 12 years, respectively, and thus can certainly benefit from effective treatment.

References


