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Treatment modalities

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This is the first 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 the diagnosis and treatment of diabetes.

Oral Agents in the Treatment of Hyperglycemia

Melander et al. (abstract 1) reported on a study of people with diabetes identified in 2 Swedish municipalities from 1984 to 1994 comparing 171 patients treated with both sulfonylurolates and metformin with 872 patients treated with sulfonylurolates alone. Total, coronary-disease, and stroke mortality levels through 1996 were increased by 77, 95, and 116%, respectively, adjusted for age, sex, duration of diabetes, municipality, year of inclusion, and fasting blood glucose at inclusion. This supports the U.K. Prospective Diabetes Study (UKPDS) finding of greater mortality among patients treated with the combination than among those treated with sulfonylurolates alone.

Emslie-Smith et al. (abstract 4) analyzed a database of 7,885 patients with diabetes in Tayside, U.K., 1,847 of whom were treated with metformin. Of those treated with metformin, 65 were admitted with myocardial infarction (MI) and 77 were admitted with congestive heart failure (CHF), but only 20% and 18% stopped metformin after admission for the respective conditions. Another 388 were treated for CHF as outpatients, and 87 had renal insufficiency. Thus, 25% of patients currently treated with metformin may have contraindications to its use.

Davis et al. (abstract 845) showed significant and independent associations of BMI, plasma glucose, lower HbA1c, serum creatinine >125 μmol/l, and metformin dose >1,500 mg daily with fasting plasma lactate levels in 184 metformin-treated patients. Lactate was <2 mmol/l in 59%, between 2 and 3 mmol/l in 34%, 3–4 mmol/l in 5%, and >4 mmol/l in 1% of the patients. The authors suggest that regular monitoring of plasma lactate may be useful with metformin treatment.

Tsaglis et al. (abstract 842) reported a fall in vitamin B₁₂ levels from 689 to 370 pmol/l and an increase in MCV (mean corpuscular volume) from 90 to 92 fl after 3 months in 24 overweight, newly diagnosed type 2 diabetic patients treated with metformin 850 mg once or twice daily. They concluded that regular monitoring of vitamin B₁₂ levels may be advisable with metformin treatment.

Two studies suggest roles of metformin treatment in patients with type 1 diabetes. Meyer et al. (abstract 849) randomized 62 patients with type 1 diabetes treated with continuous subcutaneous insulin infusion to metformin (850 mg twice daily) or placebo for 6 months. Respectively, the two groups showed an 8% decrease and a 2% increase in insulin dose, with 2.4 and 3.3 hypoglycemic events per patient per month. In a study of type 1 diabetes patients undergoing islet transplantation, Maffi et al. (abstract 119) compared 6 patients who received metformin (1.5 g daily), pioglitazone (1.2 g daily), and nateglinide (1.5 g daily) with 13 patients who received none of these drugs. Higher levels of C-peptide and lower insulin requirements in the treated group suggested improvement of islet engraftment.

Standl et al. (abstract 839) assessed 154 patients treated with glyburide (7–20 mg daily) and metformin (500–850 mg daily) randomized to miglitol (100 mg daily) or placebo for 24 weeks. HbA₁c was 8.3 and 8.6%, and 1-h glucose was 242 and 277 mg/dl, respectively. In a similar study, Maislos et al. (abstract 838) assessed 153 patients treated with metformin (1,500–2,550 mg daily) randomized to miglitol (100 mg daily) or placebo for 28 weeks. HbA₁c was 8.3 and 8.7%, and 1-h glucose 249 and 284 mg/dl, respectively. In the two studies, 10% and 8% of patients had adverse gastrointestinal effects.

Simpson et al. (abstract 836) randomized 154 insulin-treated patients to acarbose (100 mg three times daily) or matching placebo for 26 weeks. Of those treated with acarbose, 48% withdrew prematurely because of gastrointestinal side effects, compared with only 9% in the placebo group. Hypoglycemia was not increased. HbA₁c decreased 0.3% versus an increase of 0.3% on intention-to-treat analysis.

Kristensen et al. (abstract 6) reported the 1-year frequency of severe hypoglycemia to be 1.3% in 761 patients treated with repaglinide versus 3.3% in 205, 73, and 89 patients treated with the sulfonylurolates glipizide, glyburide, and gliclazide, respectively. The glucose level during hypoglycemia was <2.5 mmol/l during 7% of the episodes in the repaglinide group versus 20% of the episodes in the sulfonylurola group. HbA₁c levels were similar at 7.1–7.5%.

Thiazolidinediones

The mechanism of action of the thiazolidinediones (TZDs) remains uncertain. Kubota et al. (abstract 49) studied mice bred for deletion of the peroxisome proliferator–activated receptor gamma (PPAR-γ) to assess its biological role. Homozygotes did not survive beyond mid-embryonic

Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DPP-IV, dipeptidyl peptidase IV; EASD, European Association for the Study of Diabetes; MAGE, mean amplitude of glycemic excursion; MI, myocardial infarction; PPAR-γ, peroxisome proliferator-activated receptor gamma; QOL, quality of life; TZD, thiazolidinedione; UAE, urinary albumin excretion; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Sysème International (SI) units and conversion factors for many substances.
life. Heterozygotes fed a high-fat diet showed a 30% decrease in weight gain, with decreased food intake and less development of insulin resistance than mice with normal PPARγ. The capacity of embryonic fibroblasts from heterozygotes to differentiate into adipocytes was impaired, with pioglitazone restoring this to the level of cells with normal PPARγ.

Jacob et al. (abstract 161) studied 12 offspring of patients with type 2 diabetes homozygous for the PPARγ2 amino acid polymorphism of alanine for proline at position 12. Insulin sensitivity was 30% higher in individuals who carried the polymorphism. Thus, in two entirely different settings, a deficiency in PPARγ, perhaps leading to a decrease in intracellular lipid content, has been associated with increased insulin sensitivity, contrasting with the role of the PPARγ-agonist thiazolidinediones as insulin sensitizers.

Ide et al. (abstract 50) treated insulin-resistant ZDF rats with KRP-297, a TZD that binds to both PPARα and PPARγ, increasing oxidation of palmitic acid to normal levels in liver and skeletal muscle. Oxidation of short-chain fatty acids was not impaired and showed no change with treatment. Because long-chain, but not short-chain, fatty acids require transport of carnitine acetyltransferase I and II into mitochondria for oxidation, these enzymes may play a role in the action of the drug. KRP-297 appeared more effective than troglitazone in increasing overall whole-body insulin sensitivity, with lower fasting insulin concentrations in the treated rats. An additional potential action was reported by Lister et al. (abstract 556), showing that treatment of db/db mice with rosiglitazone, but not with metformin or glyburide, improved glycemia and increased plasma and pancreatic insulin concentrations, compatible with β-cell-protective action.

A number of studies of TZD monotherapy were reported at the EASD meeting. Grunberger et al. (abstract 8) compared 173 patients with type 2 diabetes off treatment, KRP-297, rosiglitazone (15 mg daily) or placebo. Their data showed a fall in HbA1c from 10.5 to 9.9% versus an increase from 10.3 to 11.0%, a fall in fasting glucose from 273 to 223 mg/dl versus an increase from 270 to 278 mg/dl, a fall in triglyceride from 400 to 297 mg/dl versus 335 to 317 mg/dl, and an increase in HDL cholesterol from 38 to 43 mg/dl versus from 39 to 40 mg/dl. LDL cholesterol did not increase.

Two of the studies used pooled data on monotherapy. Goldstein and Salzman (abstract 861) evaluated the efficacy of rosiglitazone (4 or 8 mg daily) versus placebo in data from three multicenter studies of a total of 2,090 patients, showing placebo-corrected falls in HbA1c of 1.1–1.8% and in fasting glucose of 29–67 mg/dl. Cranmer et al. (abstract 856) used pooled data from three multicenter studies of a total of 1,985 patients. The data showed that among patients with BMI ≥27 kg/m², rosiglitazone (4 and 8 mg/day) led to falls in fasting glucose of 36 and 52 mg/dl, while among patients with BMI <27 the falls were 23 and 45 mg/dl, suggesting increased efficacy of the agent in obese patients. Patients treated with glyburide had falls of 45 mg/dl, while placebo led to increases of 13 mg/dl.

In a study of combination therapy, Cheatham et al. (abstract 909) randomized 259 patients with type 2 diabetes to repaglinide (2 mg 3 times daily before meals), troglitazone (400 mg daily), or both for 14 weeks. HbA1c decreased from 8.9 to 7.9% with repaglinide and from 8.6 to 7.3% with the combination, but increased from 8.6 to 8.7% with troglitazone alone. Gomis et al. (abstract 851) compared 192 patients treated with sulfonylureas with 199 and 183 patients treated with sulfonylureas plus rosiglitazone (2 and 4 mg daily, respectively). HbA1c was 9.2% at baseline in all groups. It increased 0.2% in the sulfonylurea-only group and fell 0.5 and 0.9% in the sulfonylurea-plus-rosiglitazone group. Fasting glucose averaged 11.4 mmol/l initially, with an increase of 0.3 mmol/l in the sulfonylurea-only group and decreases of 0.9 and 2.1 mmol/l in the sulfonylurea-plus-rosiglitazone group.

In another study of combination therapy, Fonseca et al. (abstract 864) randomized 348 patients treated with metformin (2.5 g daily) to the addition of 4 or 8 mg rosiglitazone daily or placebo. HbA1c (8.6–8.9% at baseline) decreased 0.6 and 0.8% in the rosiglitazone group and increased 0.5% with placebo. Fasting glucose (11.9–12.2 mmol/l at baseline) decreased 1.8 and 2.5 mmol/l with the addition of rosiglitazone and increased 0.3 mmol/l with placebo. Finally, Freed et al. (abstract 866) compared urinary albumin excretion in 212 patients treated with rosiglitazone and 57 patients receiving placebo who had microalbuminuria at baseline, showing 19–28% reductions.

Fasting Versus Postprandial Glucose for Diagnosis and Treatment of Diabetes

de Courten et al. (abstract 406) screened 6,294 individuals for diabetes with an oral glucose tolerance test. Their results showed an average 20% increase in diabetes prevalence when fasting and 2-h glucose were used together in an either/or fashion rather than using either test alone for diabetes classification. Shaw et al. (abstract 156) reported on the 5- to 12-year follow-up of 595 people with previously diagnosed diabetes and 799 with newly diagnosed diabetes, of whom 243 had normal fasting glucose with 2-h glucose ≥200 mg/dl. The latter group had an increase in cardiovascular disease (CVD) and total mortality as great as that in patients with both fasting glucose >126 mg/dl and 2-h glucose >200 mg/dl, suggesting that screening programs should not use fasting glucose alone.

Costa et al. (abstract 404) screened 970 individuals at risk of diabetes, with only 57 and 21% overlap of normal and impaired glucose tolerance by the 1997 American Diabetes Association (ADA) or 1985 World Health Organization (WHO) criteria. Both groupings had similar projected 10-year cardiovascular risk, with normal, impaired, and diabetic individuals showing 8, 12, and 27% CVD risk using the WHO categorization and 8, 12, and 29% risk using the ADA categorization. Temelkova-Kurtztschiev et al. (abstract 179) studied 582 individuals without known diabetes ages 40–70 years with family history of diabetes, obesity, or dyslipidemia. After adjustment for age, sex, and HbA1c, the difference between fasting and maximal post–75 g glucose load glucose level was correlated with the carotid intima-media thickness, suggesting that postprandial glucose increments affect atherosclerosis.

At a symposium on mealtime glucose excursion, Antoine Avignon, Montpellier,
Variability of Insulin Absorption

At the symposium on glucose excursion, Lutz Heinemann, Neuss, Germany, discussed the variability of insulin absorption. Absorption is affected by a variety of factors, including the degree of obesity and the form of insulin used, but relatively few studies have assessed the variability of insulin action. With regular insulin, the intra-individual variability of a given dose based on the requirement for subsequent glucose infusion to maintain euglycemia ranges from 11% (5) to 23% (6). With longer-acting insulin preparations, this approach shows a 26–35% intra-individual variation in the amount of glucose required. Heinemann’s studies have shown that 0- to 12-h variability for NPH and ultralente insulin is approximately half that 12-24 h after the insulin dose, while insulin glargine may show greater initial variability than that 12-24 h after the dose. A further problem encountered clinically with NPH is that of incorrect resuspension technique by patients, resulting in a marked increase in variability after administration.

Hannele Yki-Järvinen, Helsinki, Finland, compared several insulin regimens for type 2 diabetes. An important finding from two of her own studies was that of the strong relationship between initial the HbA1c and the decrease occurring with treatment. For initial HbA1c increasing from 7, 9, 11, 13, and 15%, the mean fall in HbA1c was 0, 1.4, 2.8, 4.2, and 5.6%, respectively (7, 8). The best glycaemic control results for type 2 diabetes have involved basal insulin given either as NPH once or twice daily or the longer acting insulin glargine once daily, with either metformin (9) or glimepiride (10). Hypoglycaemia and weight gain are more frequent with insulin alone than with insulin and metformin in combination, and hypoglycaemia with NPH exceeds that with insulin glargine. Weight gain appears to be greater when TZDs are given with insulin.

Long-Acting Insulin

Scholtz et al. (abstract 882) administered glargine, NPH, or ultralente insulin (0.4 U/kg each) to 12 men on two occasions, with subsequent variable glucose administration to maintain blood glucose level. Glargine, NPH, and ultralente insulin produced 32, 19, and 38% variability of the required glucose infusion, respectively, during the 24 h after treatment and 23, 29, and 55% variability from 12 through 24 h. Linkeschowa et al. (abstract 880) administered glargine or NPH insulin (0.3 U/kg) to 20 patients with type 1 diabetes previously stabilized with intravenous insulin infusion, with glucose infusion to clamp levels at 7.2 mmol/l for up to 24 h (or when glucose levels exceeded 11.1 mmol/l). Onset of action was 1.1 h with glargine versus 0.7 h with NPH, and duration was 23 versus 14 h. Free insulin levels were stable at 10–12 μU/ml through 18 h with a fall to 9 μU/ml at 24 h with insulin glargine. With NPH, there was an increase from 12 to 19 μU/ml at 6 h and a decrease to 9 μU/ml at 18 h, with discontinuation at 24 h. The glucose infusion rate to maintain glycaemia was 0.6–0.9 mg · kg⁻¹ · min⁻¹ with insulin glargine through 24 h, whereas with NPH it was 3.2 mg · kg⁻¹ · min⁻¹ at 6 h, 1.0 mg · kg⁻¹ · min⁻¹ at 12 h, and discontinued at 18 and 24 h. The intersubject coefficients of variation for the area under the free insulin curve were 19 and 31%.

Ratner et al. (abstract 878) randomized 534 patients with type 1 diabetes to glargine or NPH insulin for 28 weeks, showing similar falls in HbA1c and 1.7 and 0.3 mmol/l falls in fasting glucose, respectively. Glucose <2 mmol/l was seen in 40 and 49% of patients, occurring during the night in 18 and 27%. Schoonen (abstract 883) compared insulin glargine at bedtime with human NPH insulin in the morning and at bedtime in 349 children with type 1 diabetes. Fasting glucose fell 1.3 and 0.7 mmol/l, respectively, and there were similar changes in HbA1c, and overall frequency of hypoglycaemia, although 13 and 18% of the patients experienced severe nocturnal hypoglycaemia.

Rosenstock et al. (abstract 61) treated 518 insulin-treated patients with type 2 diabetes with insulin glargine once daily at bedtime, NPH once daily at bedtime, or NPH twice daily in the morning and at bedtime, with preprandial regular insulin if required. HbA1c and fasting glucose fell similarly by 0.4 and 0.6% and 1.7 and 1.1 mmol/l, respectively. Weight gain and symptomatic nocturnal hypoglycaemia were significantly reduced with insulin glargine at 0.4 versus 1.4 kg and 31.3 versus 40.2%, respectively. In another interesting report of an approach to long-acting insulin treatment, Jørgensen et al. (abstract 876) reported the half-life of U500 and U100 NPH to be 12 and 9 h, respectively, and that of U500 and U100 semilente insulin to be 5 and 3 h, respectively, suggesting an approach to increasing duration of action of these insulin preparations.
Short-Acting Insulin

Several presentations reported studies of insulin aspart. Home et al. (abstract 60) compared 707 individuals with type 1 diabetes treated with insulin aspart with 358 individuals treated with regular insulin three times daily before meals with once or twice daily basal NPH insulin. After 6 months, HbA₁c was 0.1% lower and the prandial glucose increase was 1.2 mmol/l lower with treatment. The NPH insulin dose was 8% higher in the insulin aspart group. Major nocturnal hypoglycemic events requiring parenteral treatment occurred in 1.3% vs. 3.4% of the study subjects.

Hoogwerf et al. (abstract 892) compared 596 patients with type 1 diabetes treated with prandial insulin aspart with 286 receiving human regular insulin 30 min preprandially. Mean glucose was 8.8 vs. 10.6, 7.7 vs. 9.2, and 8.5 vs. 9.5 mmol/l after breakfast, lunch, and dinner, respectively, although predinner glucose was 8.6 vs. 8.0 mmol/l. The prandial glucose increase was 0.2 vs. 1.6 mmol/l. Major nocturnal hypoglycemia was half as frequent with insulin aspart as with regular insulin.

Klapoth et al. (abstract 870) administered microcrystalline solid insulin (87.2 U) combined with an absorption enhancer by inhalation or regular insulin (10.2 U) subcutaneously, showing maximal action at 86 and 182 min, respectively. Inhaled insulin had 49% greater action from 0–120 min but similar overall action from 0–480 min. It had a potency 12% of that of subcutaneous insulin. The variability of the metabolic effect of inhaled insulin was approximately 15%, comparable to that seen after subcutaneous injection.

Glucagon-like Peptide-1

Prentki et al. (abstract 89) reported on the effect of glucagon-like peptide-1 (GLP-1) as a growth factor in INS-1 β-cells. Phosphatidylinositide 3-kinase and PDX-1 (pancreatic and duodenal homeobox gene-1) DNA binding increased with an increase in tritiated thymidine incorporation, a marker of DNA synthesis. Bernard et al. (abstract 560) showed a 65% decrease in β-cell mass in streptozotocin-treated rats. β-cell mass doubled with 7-day GLP-1 infusion, with histological evidence of islet neogenesis. Toft-Nielsen et al. (abstract 143) studied 54 patients with type 2 diabetes and 33 control subjects for 4 h after a meal. Integrated GLP-1 and GIP (gastric inhibitory polypeptide) responses were ~80% as great in the diabetic patients and were negatively related to the degree of obesity and insulin resistance.

Maksoud et al. (abstract 738) compared insulin secretory responses to GLP-1 during hyperglycemic clamp with or without GLP-1. At 5 mmol/l glucose, C-peptide levels increased from 0.25 to 0.62 pmol/l; and at glucose 13 mmol/l, levels increased from 0.52 to 1.65 pmol/l in 12 patients with late-onset autoimmune diabetes. Levels in 12 patients with type 2 diabetes increased from 0.20 to 0.48 and from 0.61 to 1.97 pmol/l, suggesting similar potential effects in the two patient groups. Heimesaat et al. (abstract 741) administered intravenous insulin to maintain blood glucose at 78, 66, 54, and 42 mg/dl for 90 min each with and without infusion of GLP-1. C-peptide tripled during the first 30 min of GLP-1 at the 78 mg/dl glucose concentration, but then fell below basal and did not increase with GLP-1 at lower glucose concentrations, suggesting the potential safety of this treatment in stimulating insulin without causing hypoglycemia.

Dipeptidyl peptidase IV (DPP-IV) degrades the active form of GLP-1, GLP-1-(7–36), to the inactive form GLP-1-(9–36). Deacon et al. (abstract 742) administered the DPP-IV inhibitor valine-pyrrolididoe to pigs with GLP-1-(7–36), GLP-1-(9–36), or both. GLP-1-(9–36) did not affect insulin secretion or antagonize the insulinotropic effect of GLP-1-(7–36), suggesting that the increase in insulin secretion after DPP-IV inhibition is due to elevated levels of GLP-1-(7–36) rather than removal of antagonism of GLP-1-(9–36). Freyse et al. (abstract 151) administered two oral DPP-IV inhibitors to rats, showing a dose-related decrease in glycemic response to oral glucose in association with earlier and increased insulin secretion.

Balkan et al. (abstract 147) reported sustained 52% improvement of glucose tolerance by NVP-DPP728, at a dose that inhibits DPP-IV by >80%, for 6 weeks in rats with high-fat diet–induced insulin resistance, suggesting that chronic treatment with a DPP-IV inhibitor does not lead to adaptations resulting in tachyphylaxis. Knudsen et al. (abstract 744) reported on the development by Novo Nordisk of Arg34Lys26-N-(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1, with a 14-h plasma half-life, and a number of other derivatives resistant to degradation by DPP-IV after subcutaneous administration, suggesting the feasibility of once-daily administration.

Egan et al. (abstract 148) reported a >5 h insulinotropic effect of exendin-4, a peptide found in the saliva of Gila monsters, in 7 normal and 7 diabetic subjects during a hyperglycemic clamp. Exendin 4 has a long half-life compared with the 2–4 min half-life of the naturally occurring incretin GLP-1, with which it has 53% homology. Timme et al. (abstract 149) administered Exendin-4 to 7 patients with type 2 diabetes, showing duration of action up to 15 h after subcutaneous injection and with glycemic lowering. Doses of 0.1 and 0.2 µg/kg were well-tolerated, but higher doses caused nausea and vomiting. Timme et al. (abstract 144) showed the duration of satiety and fullness after a liquid meal in 8 type 2 diabetic subjects administered placebo or the GLP-1 analog exendin-4 (0.1–0.4 µg/kg s.c.) to be >8 h. Nausea was also seen, particularly with the highest dose, but peaked at 30 min, suggesting the satiety effect to be separate.
Petersen et al. (abstract 150) showed that administration of the selective glucagon antagonist BAY 27-9955 (200 mg orally) to 16 healthy young men decreased the hyperglycemic effect of hyperglycagomina. Forst et al. (abstract 751) studied the effect of C-peptide infusion administered to increase plasma levels from 0.02 to 1.3 and then to 3.5 nmol/l in 10 patients with type 1 diabetes. Plasma cGMP, an indirect measure of endothelial NO synthase activities, increased from 5.5 to 6.8 nmol/l; and erythrocyte Na⁺-K⁺-ATPase activity increased from 140 to 287 nmol phosphate - mg⁻¹·h⁻¹, showing significant correlation with plasma C-peptide level.

Johansson et al. (abstract 1226) found a 34% increase in basal forearm blood flow in 11 patients with type 1 diabetes treated with C-peptide. The NO synthase inhibitor L-NMMA (N⁴-monomethyl-L-arginine) decreased blood flow by 26% with saline versus 41% with C-peptide infusion. It blocked the vasodilatory response to acetylcholine, although it did not affect the response to nitroprusside, suggesting the vasodilatory effect of C-peptide in skeletal muscle to be NO-mediated.

Renard et al. (abstract 918) reported that monosodium L-glutamate (10 g) increased postprandial insulin secretion modestly. The response was proportional to the degree of absorption, which was <30% in 8 individuals who showed little effect, but >30% in 9 individuals studied whose insulin production increased 31%. Flesch et al. (abstract 241) reported a 1.4-fold greater 3-h glucose infusion requirement to maintain euglycemia and a 1.2-fold greater insulin secretion during the same period in 9 healthy individuals given glyburide (3.5 mg) plus enalapril (10 mg) than in the same individuals given glyburide alone, potentially indicating increased risk of hypoglycemia in diabetic patients treated with ACE inhibitors.

Approaches to Multifactorial Diabetes Treatment
Michael Berger of Dusseldorf, Germany, introduced a symposium entitled “How to Treat Type 2 Diabetes” by stressing the need for four evidence-based objectives: prevention of cardiovascular morbidity and mortality, prevention of diabetic microangiopathy, prevention of acute complications, and prevention of diabetes-related deterioration in quality of life (QOL), all without untoward side effects. “To what extent we can reach these goals,” he pointed out, “is easy to measure, to document. We can also measure microangiopathy and acute complications. More difficult is to measure the QOL, which has to be diabetes-specific and preference-weighted.”

Olaf Pedersen of Denmark discussed the Steno Diabetes Center multifactorial intervention study of 160 patients with type 2 diabetes and microalbuminuria randomized to standard treatment by general practitioners or intensive treatment by a physician-nurse-dietician team (11). Development of macroalbuminuria (urinary albumin excretion [UAЕ] >300 mg/day) was the primary end point, with retinopathy and neuropathy as secondary and mortality, stroke, MI, etc. as tertiary end points. Treatment goals for standard versus intensive treatment were HbA₁c 7.5 vs. 6.5%, cholesterol <6.5 vs. 5.0, HDL >0.9 vs. 1.1, triglyceride <2.2 vs. 1.7, and blood pressure <160/95 vs. 140/85 mmHg, respectively.

The intensive group diet was “green and low fat;” exercise for at least 30 min three times weekly was advocated, and smoking cessation counseling and nicotine replacement were provided for patients and spouses. The diabetes treatment regimen started with sulfonylureas for nonobese and metformin for obese patients, followed by combination of both treatments, and finally NPH insulin once daily added to one oral agent, with patients changed to multiple-insulin dose treatment without oral agents when >80 U/day was required. Statins or fibrates were given for dyslipidemia, and ACE inhibitors were given to all patients, with subsequent blood pressure treatment with thiazides, then calcium channel blockers, then β-blockers. Aspirin was given to all patients with evidence of CVD, and all intensive-treatment patients were given vitamin E (100 IU) and vitamin C (250 mg) daily.

After 4 years, diabetes treatment in the standard versus intensive groups used diet or oral agents alone in 43 vs. 33 patients. ACE inhibitors were given to 36 vs. 69 patients, and statins were given to 2 vs. 33 patients. The fasting glucose was 10 vs. 7.5 mmol/l, HbA₁c was 9.0 vs. 7.6%, blood pressure 144/81 vs. 136/76 mmHg, cholesterol 5.5 vs. 4.8, LDL cholesterol 3.2 vs. 2.9, triglyceride 2.7 vs. 1.8, and UAЕ 104 vs. 51 mg/day. The overall relative risk in the intensive treatment group of development of nephropathy, retinopathy, and autonomic neuropathy end points was 27, 47, and 34% that of the control group. Cardiac end points were similar, but peripheral arterial insufficiency developed in 26 vs. 10 patients. In total, 42 vs. 26 patients developed tertiary end points, and the groups had gained 0.5 and 3.6 kg, respectively. Pedersen pointed out that “the ‘broad therapeutic package’ approach is familiar to all of us and should be delivered by the general practitioners.”

R. Holman, Oxford, UK, voiced his “concern that we might neglect the treatment of glyceria, which is inherently difficult.” He discussed the UKPDS findings of 12 and 25% decreases in total diabetes and microvascular end points, a 24% decrease in cardiovascular complications, and a 21% decrease in retinopathy. In view of the significant 14% decrease in MI per 1% fall in HbA₁c in the “epidemiological analysis” of the study, Holman stated that one can argue that the fall in macrovascular end points with glycemic treatment is a real finding, despite the borderline significance of the 16% lower MI rate in the intensive treatment group. The intriguing finding that “metformin induced a greater risk reduction for identical glucose lowering” is noteworthy, and he considered the peculiar increase in risk comparing metformin plus sulfonylureas to sulfonylureas alone to be anomalous (although it was statistically significant). Interestingly, the greatest HbA₁c reduction was the fall of >2% during the first 3 months with intensive diet and 5% weight loss. Monotherapy in the intensive group further reduced HbA₁c by 0.9%.

The subsequent progressive increase in glucose levels “is not,” Holman stated, “a therapy-specific problem,” since all drugs were similar in glyceria control. “The real problem,” he continued, is the progressive decrease in β-cell function from 53 to 28% of normal during the first 6 years of treatment, with sulfonylureas and metformin associated with similar rates of decline. He insisted that “we are now duty-bound to explain this to our patients at the outset... and not to castigate them because they failed to diet.”

At a symposium on key questions emerging after the Diabetes Control and Complications Trial (DCCT) and UKPDS, David Matthews, Oxford, UK, pointed out that epidemiological study of the UKPDS data showed that having systolic blood pressure >150 mmHg and HbA₁c >8% quintupled the risk of diabetes-related end points over values <130 mmHg and 6%, respectively, stressing the “need for vigorous treatment” with “polypharmacy likely a necessity for most.”

Guntram Schernthaner, Vienna, Austria, discussed coronary heart disease (CHD) as the “leading and unsolved key...
problem of type 2 diabetes,” with its high risk of MI (12) and higher CHD mortality than in comparable patients without diabetes (13). The HOT (Hypertension Optimal Treatment) study (14) and Physicians’ Health Study (15) showed 60 and 36% CHD risks with aspirin treatment, the VAHIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial) Study showed the benefit of gemfibrozil treatment in decreasing CHD by 22% in patients with low HDL cholesterol with or without diabetes (16), and a number studies have shown the benefit of statins for lipid treatment and of a variety of approaches to blood pressure treatment.

Rury Holman, Oxford, UK, presented data on 1,703 patients during the first year after closeout of the UKPDS showing little data on 1,703 patients during the first year of a variety of approaches to blood pressure treatment. Even in this group whose general practitioners and who themselves were informed of the results of the study, without a specific intervention program, gains in glycemic control are rapidly lost, as was the case in the follow-up of the DCCT group. Henrik Mortensen, Glostrup, Denmark, presented data that among adolescents with type 1 diabetes in 1995, 60% had neuropathy, 60% retinopathy, and 15% microalbuminuria, with mean HbA1c of 9.4%, leading to an initiative to improve control by increasing the number of diabetes nurses and setting up a 24-h nurse-staffed telephone hot line for patients. Between 1996 and 1998, mean HbA1c decreased to 8.5%, microalbuminuria decreased to 10%, and there was a fall in hospitalization from 0.5 to 0.13 days per patient per year, suggesting that such treatment approaches can be initiated effectively.

In type 2 diabetes, Ann Kinmonth, Cambridge, UK, discussed the difference between the concepts of “compliance,” referring to the coincidence of a patient’s behavior with the clinical prescription, and “concordance,” the assurance that treatment is recommended that is compatible with the patient’s ability. Such a prescription requires patient-physician negotiation, in which the physician encourages the patient to ask questions, makes sure he or she is informed, and gives clear information with personal empathy. The physician and patient need to agree on the problem and have a full discussion without condoning unhealthful behavior that might be counterproductive. “While we are very used to thinking of smoking and of diet as behaviors,” Kinmonth pointed out, “we do not think about the behavior of the patient who has had the prescription given to them.” Patients can feel that the burden of treatment outweighs that of the illness, and knowledge alone does not ensure appreciation of appropriate self-care patterns. Thus, Kinmonth suggested the need for an ongoing patient-physician relationship to help the patient with type 2 diabetes follow complex therapy plans.

References