American Diabetes Association Postgraduate Course, 1996: Treatment and Prevention of Diabetes

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The first report on the 43rd Annual American Diabetes Association (ADA) Postgraduate Course discussed presentations on monitoring glucose, defining diabetes, and treating obesity. This article will address the lectures that pertained to treatment, particularly of type II diabetes.

Insulin Therapy

Bernard Zinman, Toronto, Canada, gave an interesting lecture relevant to the treatment of both types of diabetes. Zinman recalled Joslin's early assertion: "The goal of appropriate therapy for those with diabetes should include a serious effort to achieve glucose as close to the normal as feasible." More than 70 years after the first therapeutic use of insulin, we are continuing our incremental steps toward the application of this principle to the treatment of the illness. The first dose of insulin was given on January 11, 1922, but, commented Zinman, "We're still struggling to obtain physiologic replacement." A recent analysis of the Diabetes Control and Complications Trial (DCCT) results suggests that intensive treatment will add 5.2 years of sight, 6.6 years of renal function, 5.2 years of limb preservation, and 3.0 years of life to the individual who develops type I diabetes. Currently, however, 25% of individuals with type I diabetes in the U.S. are treated with one dose of insulin and 61% with two doses; therefore, at most, 14% of patients receive intensive treatment with regimens of three or four injections per day and frequent home glucose monitoring. Zinman stressed the inefficiency of our current methods of administering subcutaneous insulin. After a subcutaneous injection of regular insulin, the intrasubject coefficient of variation of the peak insulin level is 39%, and that of the time to peak is 51%. The area under the curve varies by 44%, and the variation in amount of glucose required to maintain euglycemia is 35%. Taking the latter figure as the most conservative estimate, if one administers 20 U, at times the actual dose will be 14 U and at times it will be 26 U!

Future approaches may range from changing the route of insulin administration, with intraperitoneal, intranasal, and oral dosing being explored, to genetic treatment to cause resumption of endogenous insulin secretion. A promising approach currently being explored involves the administration of modified insulins. The ideal premeal insulin will be administered immediately before eating and will have a rapid onset and a short duration of action. In contrast, the ideal basal insulin will be slow in onset, with little or no "peaking" and with a long duration of action. Both will need to be mixable and stable, with consistent kinetics of action. A candidate premeal insulin is "LysPro" insulin, with two consecutive amino acids on the B-chain, a lysine and a proline, exchanged to prevent the insulin from self-associating into the hexameric form. Zinman stated that this insulin would soon be marketed by Eli Lily under the brand name "Humalog." A "basal insulin" under development by Novo Nordisk increases the stability of the hexameric association of insulin. This Cobalt III insulin, with two cobalt atoms in the center of the hexamer, is rapidly absorbed, so variations in subcutaneous absorption are not seen. The complexes dissociate slowly in the circulation, leading to prolonged action.

Michael P. Stern, San Antonio, TX, reviewed the topic of whether exogenous insulin causes macrovascular disease. Stern began with the "bottom line" of his review: "the evidence is quite weak." Although there are several animal models suggesting atherogenic effects of insulin, the crucial question is whether "insulin is operationally in and of itself a cardiovascular risk factor." Thus, although hyperinsulinemia is a feature of "syndrome X," or the "metabolic syndrome," Stern emphasized that the underlying abnormality is insulin resistance with compensatory increases in insulin levels, with the overall syndrome rather than the hyperinsulinemia being the cardiovascular risk factor. Furthermore, although several studies have shown that insulin levels are predictors of cardiovascular disease (CVD) in men, there have been a number of negative studies, particularly when the effect of age (which in itself increases insulin levels) is factored out. As far as there being an effect of exogenous insulin, insulin dosages may be higher in some studies in individuals with diabetes who develop CVD, but these patients also have higher blood pressure and triglyceride levels. Prospective studies of the effects of insulin treatment on lipid levels show benefits. Stern pointed out, however, that the University Group Diabetes Program Study, which compared a placebo group, a fixed insulin dosage group, and a variable insulin dosage group, failed to show improved mortality in the latter group, despite an improvement in glycemia. "For people who want to believe that controlling diabetes helps CVD," Stern stated, "this is bad news." There was a trend towards lower CVD event rates in the DCCT with intensive treatment, but the numbers were small. Thus, we still cannot state with certainty whether insulin treatment is beneficial, detrimental, or neutral in terms of macrovascular disease.

Treatment of Type II Diabetes

Donald Simonson, Boston, MA, reviewed new developments in treatment for type II diabetes. Chlorpropamide, glyburide, and glipizide are the most commonly used sulfonylureas. With these agents,

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peak drug levels after oral ingestion are many times higher than necessary for glucose lowering, but there is a rapid fall-off to subtherapeutic levels. The newer glipizide formulation used in the product Glucotrol-XL does not produce high drug levels early after the dose, and blood levels are sustained for 24–48 h. Simonson characterized metformin, which has been available for close to 40 years, as causing an "anti-hyperglycemic" effect rather than causing hypoglycemia per se. It causes increased insulin sensitivity, with decreased insulin levels and decreased triglyceride levels. Recent studies suggest that the 40- to 100-fold lower risk of lactate accumulation versus that seen with phenformin can be attributed to metformin being more water soluble and hence not entering mitochondria, having a lesser effect on mitochondrial respiration. α-glucosidase inhibitors act as competitive inhibitors of the intestinal brush border enzymes required for carbohydrate absorption. Hence, these agents flatten the postprandial glucose increase—these are the first agents that inhibit postprandial glucose increases directly (rather than lowering premeal glucose levels as their primary mode of action). Lactase is inhibited much less than maltase, sucrase, or amylase, so lactose intolerance is not a commonly seen side effect. Acarbose, the most widely used drug for diabetes in Germany, has been available in Europe and Canada for about a decade; another agent, miglitol, is being developed. These drugs must be taken with meals, or, as Simonson explained, "You have to put them right on top of the mashed potatoes!" He suggested starting with a dose of 25 mg daily to minimize the side effects of bloating, cramping, and flatulence. Thiazolidinediones, the major agents being pioglitazone and troglitazone, are insulin sensitizers that are not available in the U.S. and do not reverse hyperglycemia. Simonson suggested that they may have a role in the treatment of impaired glucose tolerance (IGT) before the development of frank type II diabetes. A final group of hypoglycemic agents under development is fatty acid inhibitors, which enhance glucose metabolism by means of the Randle cycle and decrease hepatic glucose production.

Prevention of Type II Diabetes

David M. Nathan, Boston, MA, described a major new study, the Diabetes Prevention Program (DPP), which is being designed to demonstrate whether it is possible to prevent the development of type II diabetes. Diabetes is "a disease of epidemic proportions" that has been estimated to affect 15 million Americans, of whom some 1 million have type I diabetes, 7 million have diagnosed type II diabetes, and another 7 million have undiagnosed type II diabetes. In addition, there are some 11 to 18 million individuals with IGT. Type II diabetes and IGT affect 7 and 11% of the U.S. population over age 20, 10 and 13% of African-Americans, and 19 and 23% of the U.S. population age 65–74. IGT, accompanied by risk factors for macrovascular disease, may precede type II diabetes by many years, a phenomenon that has been referred to as the "ticking clock" for atherogenic lesions antedating the clinical onset of the diabetes. Thus, type II diabetes is often discovered late in its course and even later in the course of its risk factors. The Framingham Study showed a 2- to 5-fold increased risk of atherosclerotic endpoints in men and a 3- to 9-fold increased risk in women with type II diabetes. Once type II diabetes develops with fasting hyperglycemia, it is difficult to treat successfully. Furthermore, treatment of some components of the disease may worsen others: thiazides and β-blockers increasing hyperglycemia, and insulin and sulfonylureas being associated with weight gain.

Prevention of type II diabetes involves the treatment of IGT. The rationale for such treatment is that it may benefit a huge fraction of the population, analogously to our current practice of identification and treatment of dyslipidemia and hypertension. The questions to be posed in the DPP are the following: *1)* Does treatment of IGT improve outcome? and *2)* Is treatment of IGT cost-effective, taking into account the cost of the screening process? Goals will be the prevention or delay of the onset of type II diabetes, the amelioration of CVD risk factors, and, most important but perhaps most difficult to demonstrate, the prevention of CVD. The study population will be selected to be at sufficiently high risk to provide adequate statistical power within the time constraints of the planned 5- to 6-year study and to be representative of the U.S. population. Risk factors for type II diabetes that will be taken into account in selecting study subjects will include age (the risk of type II diabetes is 5–10 times greater for those over age 40 than for those under age 40), ethnicity (the incidence is greater among blacks, Hispanics, and particularly Native Americans), obesity (which conveys a 1.5–8 times greater risk), distribution of fat (central obesity has a 1.8-fold greater risk than peripheral obesity), and physical inactivity (which conveys a 1.2- to 2-fold increased risk). Conversion rates of IGT to type II diabetes are 4–9% per year in various groups, depending on these factors; therefore, with appropriate selection, a conversion rate approaching 40% should be seen in untreated patients over the course of the study. To have sufficient statistical power, the study will require 1,000 individuals in each intervention group.

The planned interventions must be effective, safe, free of side effects, readily translated into population interventions, and able to be masked for the preservation of the blinded study goals. Lifestyle interventions are effective, safe, and free of side effects, but may not be readily applied to the entire population and certainly cannot be masked. Sulfonylureas and, probably, troglitazone are effective, well tolerated, readily masked, and easily translated, but there may be significant safety concerns regarding the use of these agents in individuals with only IGT. Acarbose is effective, safe, and readily translated, but has quite common side effects and its use cannot, therefore, be easily masked. Nathan concluded, "None is perfect. We're struggling to pick the best drug."

Finally, he outlined the considerations that would be used in the cost-effectiveness analysis. Direct care costs of current treatment are relatively low, but the costs of both direct and indirect complications are high. Intensive treatment of existing type II diabetes will be higher in terms of direct care costs but probably lower in terms of costs of both types of complications. Primary prevention by treating IGT will result in decreased costs of direct care, although these costs will need to be applied to a considerably larger population. Presumably, both the direct and indirect costs of complications will be lower with this strategy. The costs of screening and those of the primary prevention intervention itself will only apply to patients treated with this strategy. The DPP is reaching the end of its planning stages, with decisions imminent on the planned interventions and an anticipated

start-up date for the trial within the next 5 months.

Diabetes Treatment in a Managed Care Setting

Any consideration of cost-effective treatment of type II diabetes must consider the delivery of diabetes care in a managed care setting. William W. Fore, Philadelphia, PA, presented a fascinating review of current directions in this field. One problem is the sheer complexity of the care of the patient with type II diabetes, involving not only glycemic control but also diet and behavior, blood pressure and lipids, and complications. Most office visits for patients with diabetes, as for those without diabetes, are allotted 10 min, and, as Fore commented, "This is a lot to do in a brief office visit." He stressed the "chaos of primary care." Most primary care physicians feel overwhelmed, overworked, and adrift in a sea of paperwork. To the delight of the audience, Fore avowed that many physicians "talk the talk, but they don't walk the walk." While recognizing that diabetes should be treated, that obesity should be treated, that hyperlipidemia should be treated, and so on, they "find it easy to take care of diabetes during the asymptomatic period. Then they refer [the patient with diabetes] when they're blind and nephrotic." He referred to surveys that show that a substantial number of physicians still use urine testing for assessment of glycemia, that only about half of patients with diabetes have an annual eye examination or cholesterol determination, and that less than one-quarter have an annual glycohemoglobin determination.

Health maintenance organizations (HMOs), groups that undertake to deliver comprehensive health service for a predetermined price to a defined panel of enrolled individuals, have changed the economics of medical treatment for health care providers. "The people that are buying your services," Fore emphasized, "have a defined amount of money. No longer is increased volume associated with increased income." Although somewhat higher initially, in "mature" markets, such defined amounts are currently just over $100 per member per year. We currently spend more than $100 billion annually for the care of individuals with diabetes, two-thirds of which is for hospitalizations. Data from a number of sources, including internal U.S. health care information, shows similar expenditures. This is about four times as much per capita as is spent for individuals without diabetes. One important aspect of "managing care" involves the selection of health care providers. Fore predicted that, eventually, such selection will take into account the costs generated by the providers. This, of course, has the potential to come into conflict with the quality of the care provided. Some studies have questioned whether macrovascular complications are related to glycemic control, and "this data is being used to argue that we can't make a difference." Furthermore, many large insurers experience 20–30% annual turnover. For this important group of patients, corporate managers may conclude that preventative medicine "doesn't pay."

Changing physician behavior by educating physicians, providing nutritionists and medical assistants to teach patients, and giving practice guidelines is clearly a slow process. In Fore's own experience with a 12-physician clinic serving some 45,000 patients, compliance with charting required data took some 18 months and introducing widespread patient education took 3 years. "When I passed out the ADA recommendations, the reaction of my primary physicians was hostility," Fore explained. He commented that these guidelines "are too complex for the real world." Other reports have documented similar experiences with provider interventions. Because of these considerations, managed care organizations that do determine it to be in their interest to optimize the treatment of diabetes may not wait for physicians to change their behavior. A number of pharmaceutical companies are providing nonphysician services. Eli Lilly has been at the forefront of such efforts. Pfizer has a "Diabetes Control Network," with toll-free telephone service to provide patient motivational services. The "Diabetes Treatment Centers of America" is another organization providing mainly nonphysician care of patients with diabetes. Merck/Medco is sending questionnaires to patients taking insulin, has a toll-free telephone service, and is planning to provide on-site provider education and telephone "case management" by nurses specializing in helping to assure that patients passing certain thresholds of illness are given appropriate services. This approach, Fore commented, "is really the way the industry is going."

"Watch out," Fore stated, "for the home health services moving into diabetes treatment." There are currently more than 17,000 such agencies, providing services to more than 3 million patients, for more than 17 million patient visits per year, a growth of 275% over the past 7 years. One explanation is cost. A home care visit costs $86. A day in a skilled nursing facility costs $293. And a day in the hospital currently costs $1,810. Currently, almost all gestational diabetic patients in Philadelphia are being seen at home. Aetna has started a home care program, "Living Well with Diabetes," with home visits by a nurse and a dietitian, triggered by either an emergency room visit or an endocrinologist visit. Examples of the services planned by this program include the following: for a new type I diabetic patient, 10 h of service and seven telephone follow-up calls; for a new type II diabetic patient, 8 h and seven calls; and for initiation of insulin for a type II diabetic patient, 6 h and three calls. In another nonphysician treatment program, Cigna of Southern California is establishing a clinic staffed by a pharmacist under supervision of an endocrinologist, allowing the pharmacist to actually prescribe medications.

Currently, some 600,000 patients with diabetes, about 8% of such patients in the U.S., see an endocrinologist, averaging about eight visits per year. If each endocrinologist had about 5,000 patient visits per year (as opposed to the current level of about 3,000) and all were for patients with diabetes, we would need about 8,000 endocrinologists in the U.S. to provide this care, more than twice the number currently practicing. However, this is not the direction of the future. We need, Fore stated, to prove that good diabetes care, with providers specializing in this field, is cost-effective, and "that risk factor reduction works." Further, he suggested that we need "more militant patient organizations."