

The symposium concluded with a panel discussion that reprised major points and addressed audience member questions. Christopher D. Saudek, MD, Program Director, served as moderator. Highlights of the discussion are presented below.

ASPIRIN USE

Dr Saudek: The Early Treatment of Diabetic Retinopathy Study (ETDRS) tested whether aspirin use would help (by its antiplatelet effect) or hurt (by causing bleeding) diabetic retinopathy. At this point, is there any evidence that aspirin is effective in treating or preventing diabetic microvascular complications?

Dr Pfeiffer: Yes. A large study evaluating aspirin use in more than 1000 patients with diabetic retinopathy found no improvement. Preliminary data from a study that is still under way suggest that aspirin is neither dangerous nor helpful to those patients.

Dr Saudek: Because of the lack of definitive evidence for an effect on diabetic microvascular complications, it seems reasonable to use aspirin in patients to prevent cardiovascular and cerebrovascular events.

AUTONOMIC NEUROPATHY

Member of the audience: There was no mention of autonomic neuropathy. Could someone comment on that?

Dr Feldman: Data are now revealing that autonomic neuropathy, similar to peripheral or somatic neuropathy, is an early manifestation of microvascular disease. It damages the small fibers primarily, and small fibers are affected quite early in the disease course.

Data also show that autonomic neuropathy is as prevalent in patients with type 2 diabetes mellitus as it is in patients with type 1 of the disease. Autonomic neuropathy is more common than previously realized, probably because of improved detection and diagnosis. A recent study conducted at the University of Utah demonstrated early and frequent occurrence: 30% of patients in the study who had impaired glucose tolerance [IGT] already had very early signs of autonomic neuropathy.

The type of autonomic neuropathy that leads to significant impairment is a later manifestation of microvascular disease, just as it is with somatic neuropathy.

Dr Saudek: Do autonomic and peripheral symmetrical polyneuropathy share the same mechanism?

Dr Malik: Few pathologic studies have been done in this regard but they did show microvascular disease in the vagus nerve and in sympathetic ganglia. However, on balance, microvascular disease is more important for distal somatic sensory neuropathy.

DIFFERING COURSES OF DIABETIC MICROVASCULAR COMPLICATIONS

Dr Saudek: The 3 major microvascular complications of diabetes mellitus—neuropathy, retinopathy, and nephropathy—seem to follow different courses. Peripheral neuropathy is seen in a substantial number of patients with very mild diabetes or even prediabetes, whereas retinopathy and nephropathy generally occur after several years of rather severe glycemic exposure. How do we explain this if the cellular mechanism for all 3 complications is the same?

Dr Malik: There is a simple answer: It depends on how each of the complications is measured. For example, before the advent of nerve biopsies, clinicians would not have known that patients with IGT could have small fiber damage. We would simply conclude that they had symptoms of neuropathy but no small fiber damage. Now we know that they do have small fiber damage.

Similarly, the markers used to identify for nephropathy—microalbuminuria and proteinuria—are good but relatively crude, and reflect later stages of disease. If renal biopsies are performed, some degree of renal damage would be found in most patients.

The diabetic microvascular complication that is easiest to detect early is retinopathy, for which signs of damage such as microaneurysms are easily identifiable

during an eye examination, which probably accounts for the higher prevalence of retinopathy (approximately 90%) than neuropathy (approximately 60%) and nephropathy (approximately 40%) in the overall diabetic population. It's a matter of how and how accurately you assess the condition.

Dr Feldman: In addition to the hypothesis that neuropathy is caused by microvascular changes, there is also the hypothesis that hyperglycemia itself adversely affects the nerves and the Schwann cells that provide nerve insulation. Animal and in vitro experiments have shown that neurons are sensitive to repeated pulses of high glucose that drop to near-normal levels, which is precisely what patients with IGT experience after eating. Most likely, the condition is a combination of microvascular disruption and tissue sensitivity that accounts for a cell's ability to handle wide fluctuations in blood glucose levels.

Dr Saudek: We have some preliminary evidence that fluctuations of blood glucose levels in everyday living are clearly abnormal, even when a person progresses from normal to mild IGT. Even before high mean blood glucose and high glycosylated hemoglobin levels developed, these patients were less tolerant of glucose and have blood glucose levels that were more variable when monitored continuously.

Dr Pfeiffer: A remarkable result of the Steno-2 study was the strong reduction in most diabetic complications, despite poor blood glucose level control with hemoglobin A_{1c} (HbA_{1c}) that was close to 8.0%. However, there was no change in autonomic neuropathy that was related to blood pressure control. Was that result seen in any other study?

Dr Feldman: In the DCCT (Diabetes Control and Complications Trial) report published in 1993, the only endpoint that did not reach statistical significance was autonomic neuropathy, possibly because it was more difficult to measure in large clinical trials than other endpoints. However, autonomic neuropathy is now easier to measure. The EDIC (Epidemiology of Diabetes Interventions and Complications) trial, which is observing patients who participated in the DCCT, will be running a complete set of autonomic function tests in these patients, along with complete nerve conduction velocity studies and quantitative tests of sensory function. The EDIC study may provide better evidence.

PROTECTIVE FACTORS

Dr Saudek: A mystery of complications associated with diabetes mellitus is the apparent "protection" from nephropathy in some people with type 1 diabetes. These patients could be observed for 50 or 60 years and not show any clinical signs of nephropathy. It may be that their blood glucose level is better controlled, but the general impression is that they are protected. Dr Pfeiffer, you presented some evidence that this protection may be familial. Do you think it is genetic or related to blood pressure or some other factor?

Dr Pfeiffer: As I suggested in my discussion, some of the studies attempted to control those factors. There is evidence that genetic influences are important. Some data from the 1970s involved 2 groups of patients with type 1 diabetes mellitus and nephropathy: patients in one group died after 15 or 16 years; patients in the other group developed a mild elevation of creatinine after 30 or 40 years of observation. Now clinicians see patients who have had type 1 diabetes for 60 years; some patients have nephropathy, but the condition is not clinically overt. My impression is that some people are protected. People who have had type 1 diabetes for 60 years have shown blood glucose levels of 300 mg/dL for 30 years and should, by natural history, have developed nephropathy if there were no such genetic component to protect them from developing the complication.

Dr Porta: There is an interesting post-study analysis of the development of retinopathy in DCCT patients by HbA_{1c} quintile, regardless of whether they had received intensive treatment or standard treatment. Among those patients with the best blood glucose level control, 10% still developed retinopathy, whereas among those patients with the poorest control, 43% did not develop retinopathy. Obviously, some factor other than metabolic control is involved.

Dr Feldman: There is currently a worldwide study that is investigating the genetic basis of diabetes mellitus and its complications. Blood serum and skin samples for genotyping are being collected from patients with type 1 diabetes and their first-degree relatives who also have type 1 diabetes. Thus far, approximately 1000 patients have been enrolled. The study goals are to gain a better understanding of the genetic factors involved in the development of nephropathy and to identify which patients will and will not develop nephropathy.

Dr Saudek: To address another factor, approximately 20% of patients with type 1 diabetes have residual C peptide and, in the DCCT, these patients seemed to have fewer diabetic microvascular complications. Some researchers have hypothesized that C peptide itself, in addition to better glucose control and better physiologic insulin release, may be protective against complications.

Currently, there is still much to be learned about diabetes and its microvascular complications. However, as we have discussed at this symposium, there are new theories, a better understanding of the molecular mechanisms involved in the development of diabetic microvascular complications, and new therapeutic approaches that intervene with these mechanisms.

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