APPENDIX 4. GLYCEMIC CONTROL

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized controlled trial designed to study the connection between glycemic control and retinal, renal, and neurologic complications of type 1 diabetes mellitus. Published results from this trial demonstrated that improved blood sugar control can delay the onset and slow the progression of DR, nephropathy, and neuropathy in type 1 patients.[116] The DCCT showed a strong exponential relationship between the risk of DR and the mean HbA1c level. For each 10% decrease in the HbA1c (e.g., from 9% to 8.1%), there was a 39% decrease in the risk of progression of retinopathy over the range of HbA1c values. There was no glycemic threshold when the risk of retinopathy was eliminated above the nondiabetic range of HbA1c (4% to 6.05%).

After 6.5 years of follow-up, the DCCT ended, and all patients were encouraged to pursue strict control of blood sugar. Most of these patients are being followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which includes 95% of the DCCT subjects. A total of 1294 to 1335 patients have been examined annually in the EDIC study. Further progression of DR during the first 4 years of the EDIC study was 66% to 77% less in the former intensive treatment group than in the former conventional treatment group.[68] The benefit persisted even at 7 years. This benefit included an effect on severe DR, including severe nonproliferative DR (NPDR), proliferative DR (PDR), CSME, and the need for focal/grid or panretinal laser photocoagulation surgery.[70] The decrease in HbA1c from 9% to approximately 8% did not drastically reduce the progression of DR in the former conventional treatment group, nor did the increase in HbA1c from approximately 7% to approximately 8% drastically accelerate DR in the former intensive treatment group.[68] Thus, it takes time for improvements in control to negate the long-lasting effects of prior prolonged hyperglycemia, and once the biological effects of prolonged improved control are manifest, the benefits are long-lasting. Furthermore, the total glycemic exposure of the patient (i.e., degree and duration) determines the degree of retinopathy observed at any one time.

A positive relationship between the 4-year incidence and progression of retinopathy and glycosylated hemoglobin remains after controlling for other risk factors, such as duration of diabetes and severity of retinopathy at a baseline examination.[93, 94, 172] Extrapolation of pathologic and clinical experience strongly suggests that poor levels of control contribute to microangiopathy, including retinopathy.[422] The development of PDR parallels an increased risk of nephropathy, myocardial infarction, and/or cerebral vascular accidents.

Although good glycemic control is advised, there is some evidence that rapid improvement of long-standing poor control may increase the risk of retinopathy progression over the first year for some patients. About 10% of patients with type 1 diabetes who had initial retinopathy at the beginning of the DCCT had increased retinopathy progression.[423] Specifically, there may be a transient increase in the number of cotton wool spots seen on retinal examination. Frequent ophthalmologic monitoring is important when diabetic patients are being brought under better metabolic control.[423]

In the DCCT there was a threefold increase in severe hypoglycemic events and excess weight gain among patients using intensive treatment regimens. Increased risk of hypoglycemia is a consequence of strict blood glucose control. Irregular food intake, failure to check blood glucose before planned or unplanned vigorous exercise or before operating a motor vehicle, and excess alcohol are risk factors for hypoglycemia. Diabetes mellitus education and regular reinforcement should be provided by diabetes nurses and dietitian educators and may help minimize the risk of hypoglycemia. Increasing use of semaglutide (Ozempic®, Novo Nordisk, Inc Plainsboro, NJ), a recently approved glucagon-like peptide-1 receptor agonist used to treat patients with type 2 diabetes mellitus, can result in rapid glycemic control and severe hypoglycemia and has been reported to cause significantly higher rates of retinopathy complications in patients.[424]

The United Kingdom Prospective Diabetes Study (UKPDS),[71, 167] a randomized controlled clinical trial of blood glucose control, enrolled 3867 patients with newly diagnosed type 2 diabetes. Intensive blood glucose control by either the sulfonylureas or insulin decreased the risk of microvascular complications but not the risk of macrovascular disease. There were no adverse effects of the individual drugs on the cardiovascular outcome. In this study, there was a 29% reduction in the need for retinal photocoagulation in the group that had intensive glucose therapy compared with those that had conventional treatment (relative risk, 0.71; 95% CI, 0.53–0.96; $P = 0.003$).

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was a large clinical trial of adults with established type 2 diabetes who are at especially high risk of cardiovascular disease (CVD).[128] Type 2