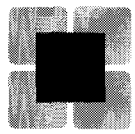

Tight blood glucose control: Is it worth it?

BYRON J. HOOGWERF, MD

■ Several investigations have assessed the relationship between glycemic control and complications in diabetes mellitus. Key evidence is reviewed that supports the beneficial effects of "tight" blood glucose control. Pertinent animal data show that good blood glucose control is associated with less retinopathy and nephropathy and fewer congenital anomalies in offspring. Short-term studies in humans show similar trends in microvascular complications and pregnancy. Similarly, peripheral neuropathy may be lessened with lower blood glucose. Although no studies have demonstrated a reduction in atherosclerotic disease with improved glycemic control, dyslipidosis frequently improves, which should reduce the risk for coronary heart and peripheral vascular disease.

□INDEX TERMS: BLOOD GLUCOSE; DIABETES MELLITUS □CLEVE CLIN J MED 1990; 57:390-395

DIABETES MELLITUS is estimated to cost this country more than $20 billion per year in health dollars and lost income. The disease affects more than 5% of the population, all of whom face the risk of devastating complications. Effective management of diabetes presents a challenge to clinicians in terms of patient education and compliance that is unparalleled by other disorders.[1-4]

Superimposed on the practical difficulties of management is the unresolved issue of whether aggressive attempts to control blood glucose will have an impact on the development of complications. Achieving tight blood glucose control is labor-intensive and costly, requiring much time from physicians, nutritionists, and nurse-educators. Patients must invest time in learning to manage their diabetes and in monitoring their glucose levels several times a day. Frequent visits to health care professionals, laboratory follow-up, and buying and using monitoring equipment contribute to the high cost. Hence, the dilemma for both physician and patient: Are the time, effort, and expense of achieving tight control of blood glucose justified by a reduction in the risk of long-term complications?

Among the complications of diabetes, retinopathy is the leading cause of blindness in young people and the second leading cause overall. Diabetic nephropathy is a substantial contributor to the total number of patients who require dialysis or transplantation. Diabetes is the leading cause, other than trauma, of lower extremity amputations necessitated largely by neuropathy-related injuries and ischemic lesions. Finally, diabetes more than doubles the risk for atherosclerotic cardiovascular disease and is associated with increased mortality in persons who have myocardial infarctions.

The outcome of prospective studies, including the Diabetes Control and Complications Trial,[5,6] will help to resolve issues about the impact of glycemic control on the risk for complications. Extensive reviews published in the past several years[7-9] also help to clarify these issues. This article presents pertinent evidence that tight blood glucose control is beneficial.

From the Department of Endocrinology, The Cleveland Clinic Foundation.

Address reprint requests to B.J.H., Department of Endocrinology, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

ANIMAL STUDIES

The best animal studies have looked at the effect of controlling hyperglycemia on the progression of microvascular complications of diabetes as well as the effect of hyperglycemia on the developing fetus in the diabetic animal. Engerman and colleagues provided the most dramatic evidence that rigorous glycemic control in diabetic dogs reduces the risk for microaneurysms.[10] They studied 20 diabetic and 10 nondiabetic animals during 5 years in which tight glycemic control was maintained in half of the diabetic animals. At the end of 5 years, the animals' eyes were enucleated and studied for diabetes-related retinal changes. There were clearly fewer diabetes-related changes in the 10 animals with better glycemic control.

One limitation of such studies is that proliferative retinopathy does not develop in animals, so there is no model for the more advanced stages of diabetic retinopathy.

The landmark studies of Mauer and associates on histologic changes of diabetic nephropathy in rats provided some of the earliest evidence of the benefits of good blood glucose control.[11,12] Mesangial matrix thickening, one of the most sensitive measurements of diabetes in the rat kidney, was reduced by improving blood glucose control with islet cell transplants. Mauer's data were subsequently confirmed by Orloff and co-workers.[13]

In addition to the microvascular complications of diabetes, animal studies have also looked at the effects of hyperglycemia on the developing fetus in diabetic animals.[14,15] These studies showed an increased incidence of congenital anomalies most likely attributable to the hyperglycemia rather than some other metabolic defect. Improved glycemic control reduced the risk of those anomalies,[16] which in the animals were similar to those in children of diabetic mothers.

HUMAN STUDIES

The largest body of clinical data analyzed is that of Pirart,[17] who reported on his own clinical experience with more than 4,000 diabetic patients followed over more than two decades. Based on serial urine and blood glucose determinations in his clinic, he divided his patients into two groups: those with better and those with poorer blood glucose control. He considered all the major complications of diabetes and adjusted their prevalence for known duration of disease.

In Pirart's study, microvascular complications, neuropathy, and atherosclerotic disease were more frequent and more severe with longer-standing diabetes and with poorer blood glucose control. Although his data have been criticized for not being "randomized," his conclusions lend strong support to an association between poor glycemic control and increased risk of complications.

Retinopathy

The prospective study by Job and colleagues[18] is one of the earliest to associate reduced microaneurysms with presumed improvement in blood glucose control in patients receiving multiple insulin injections. Although this study's methodology has been criticized, a number of other prospective studies have supported the conclusions. Most of these studies achieved tight control in type I diabetic patients with multiple insulin injections or chronic subcutaneous insulin administration (insulin pumps). The data of Rosenstock and associates[19] confirm the relationship between less retinal change and tighter blood glucose control. These patients were self-selected and not randomized, but short-term randomized studies have also supported this concept.[20–22]

Rapid improvement of blood glucose is associated with short-term worsening of diabetic retinopathy immediately after intensive control is begun.[23] The mechanism for this phenomenon is not understood, but the effects do not seem to be long lasting.

The report by Ramsay and colleagues[24] on pancreas transplant recipients suggests an improved outcome in the eyes in these patients, most of whom had other microvascular complications, including end-stage renal disease. Studies of pancreas transplantation have great appeal because, with functioning pancreatic grafts, there is much more consistent near-normalization of blood glucose than with most other insulin-intensification regimens.[25,26]

Finally, the carefully obtained data from the Wisconsin-based retinopathy study show that the rate of progression of diabetic retinopathy over a 4-year follow-up is related to glycated hemoglobin values, no matter how long the patient has had diabetes.[27]

Nephropathy

Several observations provide evidence that good blood glucose control reduces the risk of diabetic nephropathy. First, in prospective randomized studies, patients who have achieved good blood glucose control show reduced albumin excretion, which is an early marker of diabetic nephropathy, and lower creatinine levels.[19,21,22].

Increased glomerular filtration rate (GFR), which translates to increased "intra-renal pressure" may be a

mechanism for nephropathy that is also related to hyperglycemia.[28] It is well known that, from the onset of diabetes, patients with poorly controlled blood glucose have elevated GFRs which improved blood glucose control can reduce to a normal range. The consequence of elevated GFR may be kidney damage comparable to that seen in the remnant kidney models described by Hostetter and colleagues.[29]

Abouna and colleagues'[30] anecdote of transplanting two kidneys with established diabetic nephropathy into normoglycemic recipients and subsequent biopsy demonstration of improvement provides limited but tantalizing evidence of the effects of normoglycemia on the kidney.

Finally, biopsy data obtained from pancreas transplant recipients also indicate that this level of glycemic control may improve the histologic changes associated with diabetes.[31,32]

Neuropathy

Studies of diabetic neuropathy are much more limited than those of retinopathy or nephropathy; however, it can be observed clinically that improved glycemic control reduces the pain of neuropathy. One of the commonly accepted mechanisms for diabetic neuropathy is that of nerve damage from sorbitol accumulation in the nerve.[33] The conversion of glucose to sorbitol via aldose reductase is directly related to the substrate (glucose) concentration. By inference, lower glucose would reduce sorbitol accumulation with benefits similar to those seen with aldose reductase inhibitors.[34,35]

Studies that have looked at the effects of blood glucose control, through either insulin injections[36] or pancreas transplantation,[37] show beneficial effects on nerve function.

Macrovascular disease

There are no good studies showing that improved glycemic control reduces the risk of macrovascular disease. The University Group Diabetes Program (UGDP) was a prospective study designed to answer this question.[38] The UGDP originally had five patient groups with type II diabetes mellitus and was intended to compare variable-dose insulin, fixed-dose insulin, tolbutamide, a tolbutamide placebo, and phenformin (the variable-dose insulin regimen was designed to achieve lower sugars than the fixed-dose regimen). Because of an apparent increased number of cardiac events in the tolbutamide group, this arm of the study was discontinued. It was not resolved whether the cardiac events were related to the drug therapy or to an increase in other risk factors for coronary heart disease.[39] The insulin-treated groups showed no difference in cardiovascular risk as a function of glycemic control[40]; however, the numbers of patients were likely too small to demonstrate a difference, given the duration of the trial.

Still, evidence is accumulating that lipid profiles became less atherogenic with improved blood glucose control. With better control, there is a reduction in triglycerides, frequently an elevation in HDL cholesterol, and, in many cases, a reduction in LDL cholesterol. Because evidence is clear that these changes reduce the risk of coronary heart disease, we can infer that improved blood glucose control also offers this benefit.

Pregnancy

The data are now compelling that good blood glucose control improves the outcome of pregnancies of diabetic mothers. A pregnant woman with diabetes faces two major risks: increased likelihood of congenital anomalies and increased risk of spontaneous abortion or perinatal mortality. These problems occur more frequently as glycated hemoglobin levels increase.[41] A direct correlation has been shown between the incidence of congenital anomalies and the level of glycated hemoglobin at the time the pregnancy is confirmed[42]; when glycated hemoglobin levels are normal at the time of conception, the risk of congenital anomalies is essentially the same as for nondiabetic mothers.

Because hyperglycemia has major adverse effects on the fetus early in the pregnancy, it is imperative to make every effort to normalize blood glucose *before conception*.[43] This is a critical consideration for all diabetic women who anticipate future pregnancy. Once good blood glucose levels are achieved, they can be maintained throughout the pregnancy with reasonable effort. It is common clinical experience for pregnant women to become highly motivated—at least for the duration of the pregnancy—to achieve normal or near-normal blood glucose levels. Good control, which is associated with less risk of ketosis, also reduces the risk of spontaneous abortions.[44–46]

ACHIEVING GOOD GLUCOSE CONTROL

Achieving good blood glucose control depends on the methods of control and monitoring. The body of information and recommendations about methods of control is growing rapidly. The accumulating information about the proper dietary composition for patients with diabetes is increasingly specific and practical. The benefits of exercise, both in facilitating weight loss and im-

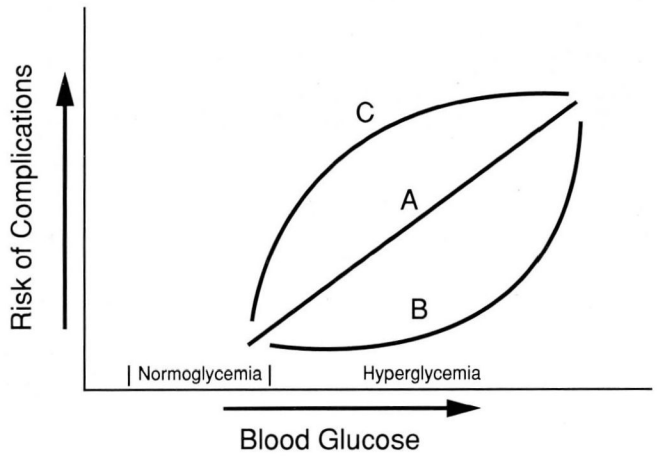

FIGURE 1. Possible relationships between blood glucose level and the risk of complications. Line A represents a linear relationship. Line B represents a relationship in which marked hyperglycemia is necessary for complications to develop. In the relationship represented by line C, slight elevations in blood glucose markedly increase the risk of complications; in this setting, the level of control typically viewed as acceptable would be inadequate.

proving blood glucose control, have been studied extensively. In addition, pharmacotherapy—particularly insulin—is better, with improved purity and the availability of human insulins and insulin pumps. We also have a better understanding of how to mix insulins in an effort to mimic pancreatic secretion of insulin.

Monitoring methods also have improved in recent years. Two important advances have been the ability to determine glycated hemoglobin levels, which reflect mean blood glucose levels over a period of about 2 months, and capillary-based blood glucose (fingerstick) determinations that the patient can self-administer. Self-monitoring of blood glucose has become progressively less expensive and remarkably accurate, considering the size and cost of the devices. This new technology allows patients to adjust their own medication, and it seems to improve compliance with diet and exercise regimens.

UNRESOLVED ISSUES

Although the weight of evidence from animal and human studies supports the concept of improved glycemic control, a number of issues remain unresolved. For example, the relationship between glycemic control and the risk of complications is unclear. If the relationship is linear, as suggested by studies of congenital anomalies, then any improvement in blood glucose control will achieve some reduction in the risk of complications of diabetes (*Figure 1*). If relatively high levels of blood glucose are necessary for complications to accelerate, then it should be satisfactory to maintain the mean blood glucose level below this high level. On the other hand, if the risk of complications accelerates with only small increases in blood glucose, then our current efforts are likely to be ineffective since it is difficult, at best, to achieve normoglycemia in most patients with diabetes. Until we have answers to these questions, it is prudent to assume a linear relationship and strive to achieve blood glucose levels as close to normal as possible.

Also to be resolved is whether the potential adverse effects of attempting rigorous glycemic control may counterbalance the benefits. It is well known that, in type I diabetic patients, consistent efforts to lower blood glucose increase both the frequency and severity of hypoglycemic episodes and, thus, the number of major insulin reactions. Whether there are long-term sequelae of such hypoglycemic episodes is as yet unknown. It does not appear, however, that short-term hypoglycemia has any major neurologic sequelae.

It is also unclear whether improved blood glucose control has the same benefit at all stages of development of complications. The data from Orloff and colleagues[13] suggest that, in animals, improved control may have beneficial effects at all stages of development of diabetic nephropathy. Nevertheless, it is not clear that patients with end-stage renal disease, proliferative retinopathy, or profound neuropathy will achieve the same benefit, especially in the short term, as those with less well-established complications.

The observation that some long-lived proteins may be glycated suggests that some complications may not be as readily reversible in the face of long-term hyperglycemia. These advanced glycation products are potential culprits in a number of complications of diabetes.[46] However, the contribution of such glycation to complications and their reversibility are not clearly understood.[47,48] The Diabetes Control and Complications Trial is designed to address this question by studying subjects who lack clinical evidence of microangiopathy and subjects with early diabetic microangiopathic changes.[5,6]

Some patients (and some physicians) remain skepti-

cal about the potential benefits of rigorous blood glucose control, and prospective studies are underway to address some of these issues.[5,6] Meanwhile, it seems prudent to base our practice on the weight of current evidence, which clearly supports the benefits of improved blood glucose control. No study has ever demonstrated that hyperglycemia of any degree benefits the animal or human who has it!

ACKNOWLEDGMENTS

The author thanks Dr. Angelo Licata for his review and comments and S. Dodich for help in the preparation of this manuscript.

REFERENCES

1. Physicians Guide to Insulin Dependent (Type I) Diabetes: Diagnosis and Treatment. Alexandria, VA, American Diabetes Association, 1988.
2. Physicians Guide to Non-Insulin-Dependent (Type II) Diabetes: Diagnosis and Treatment, 2nd ed. Alexandria, VA, American Diabetes Association, 1988.
3. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; **28:**1039–1057.
4. Harris MI, Hadden WE, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose levels in U.S. population age 20–74 years. Diabetes 1988; **36:**1595–1607.
5. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase. Diabetes 1986; **35:**530–545.
6. The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care 1987; **10:**1–19.
7. Leslie ND, Sperling MA. Relation of metabolic control to complications in diabetes mellitus. J Pediatr 1986; **108:**491–497.
8. Hanssen KF, Dahl-Jorgensen K, Feldt-Rasmussen B, Brinchmann-Hansen 0, Deckert T. Diabetic control and microvascular complications: the near-normoglycaemic experience. Diabetologia 1986; **29:**677–684.
9. Raskin P, Rosenstock J. Blood glucose control and diabetic complications (review). Ann Intern Med 1986; **105:**254–263.
10. Engerman R, Bloodworth JMB Jr, Nelson S. Relationship of microvascular disease in diabetes to metabolic control. Diabetes 1977; **26:**760–769.
11. Mauer SM, Sutherland DER, Steffes WW, et al. Pancreatic islet transplantation: effects on the glomerular lesions of experimental diabetes in the rat. Diabetes 1974; **23:**748–753.
12. Mauer SM, Steffes MW, Sutherland DERE Najarian JS, Michael AF, Brown DM. Studies of the rate of regression of glomerular lesions in diabetic rats treated with pancreatic islet transplantation. Diabetes 1975; **24:**280–285.
13. Orloff MJ, Yamanaka N, Greenleaf GE, Huang Y-T, Huang D-G, Leng X-S. Reversal of mesangial enlargement in rats with long-standing diabetes by whole pancreas transplantation. Diabetes 1986; **35:**347–354.
14. Eriksson U, Dahlstrom E, Larsson KS, Hellerstrom C. Increased incidence of congenital malformations in the offspring of diabetic rats and their prevention by maternal insulin therapy. Diabetes 1982; **31:**1–6.
15. Funaki K, Mikamo K. Developmental-stage-dependent teratogenic effects of matenal spontaneous diabetes in the Chinese hamster. Diabetes 1983; **32:**637–643.
16. Baker L, Egler JM, Klein SH, Goldman AS. Meticulous control of diabetes during organogenesis prevents congenital lumbosacral defects in rats. Diabetes 1981; **30:**955–959.
17. Pirart J. Diabetes mellitus and its degenerative complications:a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978; **1:**168–88, 252–263.
18. Job D, Eschwege E, Guyot-Argenton, Aubry JP, Tchobroutsky G. Effect of multiple daily insulin injections on the course of retinopathy. Diabetes 1976; **25:**463–469.
19. Rosenstock J, Friberg T, Raskin P. Effect of glycemic control on microvascular complications in patients with type I diabetes mellitus. Am J Med 1986; **81:**1012–1018.
20. Lauritzen T, Frost-Larsen K, Larsen HW, Deckert J. Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin dependent diabetes. Lancet 1983; **1:**200–204.
21. The Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. N Eng J Med 1984; **311:**365–372.
22. Holman RR, Dornan TL, Mayon-White V, et al. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. Lancet 1983; **1:**204–208.
23. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O, Aker Diabetes Group. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J 1985 **290:**811–815.
24. Ramsay RC, Goetz FC, Sutherland DER, et al. Progression of diabetic retinopathy after pancreas transplantation for insulin-dependent diabetes mellitus. N Engl J Med 1988; **318:**208–214.
25. Pozza G, Secchi A, Bosi E, et al. Artificial insulin delivery systems versus pancreas transplantation: effect on metabolic control. Transplant Proc 1985; **17:**358–359.
26. Sutherland DER, Goetz FC, Najarian JS. One hundred pancreas transplants at a single institution. Ann Surg 1984; **200:**414–440.
27. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 1988; **260:**2864–2871.
28. Noth RH, Krolewski AS, Kaysen GA, Meyer TW, Schambelan M. Diabetic nephropathy: hemodynamic basis and implications for disease management (Davis Conference). Ann Intern Med 1989; **110:**795–813.
29. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med 1982; **72:**375–380.
30. Abouna GM, Al-Adnani MS, Kremer GD, Kumar SA, Daddah SK, Kusma G. Reversal of diabetic nephropathy in human cadaver kidneys after transplantation into nondiabetic recipients. Lancet 1983; **2:**1274–1276.
31. Bilous RW, Mauer SM, Sutherland DER, Najarian JS, Goetz FC, Steffes MW. The effects of pancreas transplantatation on the glomerular structure of renal allografts in patients with insulin-dependent diabetes. N Engl J Med 1989; **321:**80–85.
32. Bohman SO, Tyden G, Wilczek H, et al. Prevention of kidney graft diabetic nephropathy by pancreas transplantation in man. Diabetes 1985; **34:**306–308.
33. Finegold D, Lattimer SA, Nolle S, Bernstein M, Greene DA. Polyol pathway activity and myo-inositol metabolism: a suggested relationship in the pathogenesis of diabetic neuropathy. Diabetes 1983; **32:**988–992.
34. Greene DA, Lattimer SA, Sima AAF. Are disturbances of sorbitol, phosphoinositide, and Na^+ -K^+–ATPase regulation involved in the pathogenesis of diabetic neuropathy. Diabetes 1988; **37:**688–693.
35. Judzewitsch RG, Jaspan JB, Polonsky KS, et al. Aldose reductase inhibition improves nerve conduction velocity in diabetic patients. N Engl J Med 1983; **308:**119–125.
36. Young RJ, Macintyre CCA, Martyn CN, et al. Progression of subclinical polyneuropathy in young patients with type I (insulin-dependent) diabetes: associations with glycaemic control and microangiopathy (microvascular complications). Diabetologia 1986; **29:**156–161.
37. Kennedy WR, Navarro X, Goetz FC, Sutherland DER, Najarian JS. Effects of pancreatic transplantation on diabetic neuropathy. New Engl J Med 1990; **322:**1031–1037.
38. University Group Diabetes Program. A Study of the effects of hypoglycemic agents on vascular complications in patients with adult-

onset diabetes. VII. Mortality results. Diabetes 1970; **19(suppl 12):**785–830.
39. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII. Mortality and selected non-fatal events with insulin treatment. JAMA 1978; **240:**37–42.
40. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VIII. Evaluation of insulin therapy: final report. Diabetes 1982; **31(suppl 15):**1–81.
41. Key TC, Giuffrida R, Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. Am J Obstet Gynecol 1987; **156:**1096–1100.
42. Fuhrmann K, Reiher H, Semmler K, Fischer M, Glöchner E. Congenital anomalies: etiology, prevention, and prenatal diagnosis. [In] Jovanovic, Peterson, Fuhrmann, eds. Diabetes and Pregnancy: Teratology, Toxicity, and Treatment. New York, Praeger, 1984.
43. Furhmann K, Reiher H, Semmler K, Fischer F, Fischer M, Glockner E. Prevention of congenital malformations in infants of insulin-dependent diabetic mothers. Diabetes Care 1983; **6:**219–223.
44. Hadden DR. Diabetes in pregnancy 1985. Diabetologia 1986; **29:**1–9.
45. Freinkel N, Dooley SL, Metzger BE. Care of the pregnant woman with insulin-dependent diabetes mellitus. N Engl J Med 1985; **313:**96–101.
46. Brownlee M, Vlassara H, Cerami A. Non-enzymatic glycosylation and the pathogenesis of diabetic complications. Ann Intern Med 1984; **101:**527–537.
47. Monnier VM, Vishwanath V, Frank KE, Elmets CH, Dauchot P, Kohn RR. Relation between complications of type I diabetes mellitus and collagen-linked fluorescence. N Engl J Med 1986; **314:**403–408.
48. Vishwanath V, Frank KE, Elmets CA, Dauchot P, Monnier VM. Glycation of skin collagen in type I diabetes mellitus: correlation with long-term complications. Diabetes 1986; **35:**916–921.