

Effect of Blood Glucose Concentrations on the Development of Chronic Complications of Diabetes Mellitus

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Diabetes is associated with increased risk of cardiovascular disease, coronary heart disease, stroke, acute myocardial infarction, blindness, and renal failure. Strategies to reduce their occurrence are an essential focus of patient care. More than one pathogenic process is involved, and genetics influence the risk. Hyperglycemia is a factor in the development of microvascular and possibly macrovascular complications. Two possible mechanisms of glucose damage are glycation of proteins and the polyol pathway. Research led to the identification of drugs that block parts of the pathways. In clinical trials, intensive control of blood glucose concentrations decreased the risk of microvascular complications. Adverse effects associated with intensive therapy, however, include hypoglycemia and weight gain.
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OUTLINE

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Diabetes mellitus is associated with 2-3 times the risk of cardiovascular disease, coronary heart disease and stroke¹ and is implicated in 25% of acute myocardial infarctions.² It is the leading cause of blindness in the United States and of renal failure.^{2,3} Individuals with diabetes are 2.5 times more likely to be hospitalized than those without the disease.² Overall, it is estimated that the cost of diabetes in the United States is \$92 billion/year.²

Epidemiologic and clinical data showed an association between hyperglycemia and the complications of diabetes.³⁻⁶ Diagnostic criteria

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for diabetes are based on the relationship between hyperglycemia and retinopathy, nephropathy, and macrovascular disease.⁷ The degree of glycemic control contributes to the risk of nephropathy and retinopathy in patients with type 1 disease.⁶ Approximately 25% of people with diabetes never develop chronic complications regardless of glycemic control, whereas approximately 5% develop severe complications within a few years of diagnosis.⁸ Hypertension and hyperlipidemia occur frequently and contribute to vascular disease.⁸

Mechanisms of Damage from Hyperglycemia

Identifying the mechanisms by which glucose causes damage may be helpful in developing ways to prevent complications. It is likely that more than one pathogenic process is involved, and the critical process may vary with the complication.⁹ Furthermore, there is an apparent genetic influence on the risk of complications.

Many physiologic abnormalities have been associated with hyperglycemia. Acute effects include elevated protein kinase C activity, hyperlipidemia, alterations in renal hemodynamics, abnormalities in prostacyclin activity, rheologic abnormalities, and hypersensitivity of platelets.¹⁰⁻¹² Many of these disorders are reversible with correction of hyperglycemia.^{10, 11} Therefore, it is not known why they may progress, or even

appear for the first time, after glucose is corrected.¹³ Two possible mechanisms of long-term glucose toxicity are glycation of proteins and the polyol pathway. Research into each mechanism has been the impetus for the development of new drugs.

Glycation of Proteins

Glucose and proteins undergo a complex series of reactions that ultimately results in irreversible alterations in tissue structure and interference with normal protein function. For this reason, glycation of proteins was proposed as an explanation for so-called hyperglycemic memory, or continued destruction of tissues after restoration of glycemic control.¹³ Some individuals may produce enzymes capable of metabolizing precursors of glycated proteins to result in less harmful molecules.¹⁴ This is also a possible explanation for genetic differences in risk of complications; that is, those who can efficiently clear glycated proteins may be at decreased risk compared with those who cannot.

Decreased renal clearance of glycated proteins may be involved in acceleration of some complications in patients with declining renal function. The glycation sequence, which is not completely described, begins when sugar molecules undergo nucleophilic addition reactions with free amino groups on proteins to form molecules called Schiff bases (Figure 1).¹⁵ Because the reaction is nonenzymatic and reversible, these early glycated proteins are formed in proportion to the surrounding glucose concentration. The reaction is rapid and reaches equilibrium within hours.¹⁵ These compounds are unstable and undergo further rearrangement to the Amadori product (1-amino-1-deoxy-D-ketose).¹³

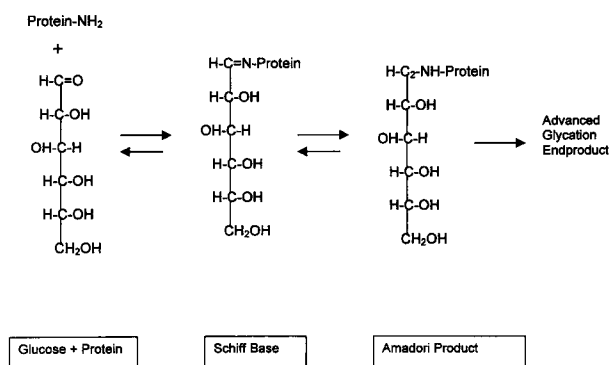


Figure 1. Proposed steps in the formation of glycated end products.

Reactions involved in formation of Amadori compounds are also reversible, although slower, reaching equilibrium in several weeks. The concentration of Amadori compounds is related to mean blood glucose concentration over the previous weeks. Amadori products eventually degrade, resulting in carbonyl compounds that are highly reactive with free amino groups. These ultimately form complexes known as intermediate and advanced glycated end products (AGEs) or advanced glycated proteins (AGPs). Once AGEs have formed, the process is irreversible. Therefore, the concentration of AGEs is a reflection of overall glucose concentration throughout life. These reactions occur in everyone to an extent determined by blood glucose concentrations. Normally, the process may be involved in tissue remodeling and removal of aging macromolecules from the circulation.¹⁶ This may explain why some chronic complications of diabetes resemble acceleration of the aging process.

Several mechanisms have been identified by which AGEs interfere with normal tissue function. Some abnormalities in diabetes may result from AGEs attaching to proteins of the extracellular matrix. The extracellular matrix is widened in all types of vessels in diabetes, including basement membranes of the retinal and vasa nervorum, and mesangial matrix of the glomerulus.¹⁷ Alterations in the structure of basement membrane may result in part by binding of AGEs to type IV collagen and laminin, interfering with their ability to self-assemble and associate with other basement membrane macromolecules.^{18, 19} Other consequences of glycation cause the basement membrane to be less susceptible to normal proteolytic degradation and inactivation of nitric oxide.²⁰⁻²²

Further problems are caused by AGEs on collagen in vessel walls that have increased binding to low-density lipoprotein (LDL) and immunoglobulin G (IgG).^{23, 24} Bound LDL and IgG are likely to react further with glucose and glycated proteins to form additional AGEs. Thickening of vessel walls is in part a direct consequence of the accumulation of these bound proteins.¹⁷ In addition, macrophages and monocytes have receptors that interact with AGEs, triggering release of cytokines such as tumor necrosis factor and interleukin-1, and ultimately the release of growth factors.¹⁶ These processes are involved in formation of atherosclerotic plaques.²⁵ Release of these factors and diminished activity of nitric oxide may also contribute to the cellular proliferation associated

with retinopathy, nephropathy, and neuropathy.^{17, 26}

Binding of AGEs to receptors on endothelial cells induces changes in coagulation pathways that promote thrombosis and stimulates production of endothelial-1, which has vasoconstrictive activity. A separate mechanism of AGE-induced damage involves glycation of DNA and RNA, which results in mutations and abnormal expression of genes in experimental models.²⁷⁻²⁹

Several agents were investigated for activity in inhibiting AGE development. Pimagidine is an investigational drug that interferes with formation of AGEs and may have other actions as well.³⁰ Its efficacy was shown in studies in animal models of retinopathy and nephropathy. In an open label study in 18 humans with diabetes, hemoglobin AGE concentrations decreased significantly during 1 month of treatment with pimagidine.³¹ A large randomized, double-blind study of the drug is under way.¹⁴ If pimagidine proves to be reasonably safe and effective, it may play a role as an adjuvant to intensive efforts to control blood glucose. Other compounds, such as thiamine pyrophosphate and pyridoxamine, also block AGE formation and are under investigation for this indication.³² Antioxidants reduce AGE formation,³³ and vitamin E has variable efficacy in reducing protein glycation.^{34, 35}

Polyol Pathway and Myoinositol

In the polyol pathway, aldose reductase catalyzes the reduction of glucose to sorbitol, which is then oxidized to fructose by sorbitol dehydrogenase (Figure 2). This is a minor pathway in individuals with normoglycemia, but accounts for significant glucose disposal in the presence of hyperglycemia. Specifically, it is important in noninsulin-dependent cells that take up glucose in proportion to blood concentration. Sorbitol does not traverse cell membranes as easily as does glucose and accumulates in affected cells.³⁶ Some chronic complications of diabetes, such as retinopathy, nephropathy, and neuropathy, are manifested in tissues that include noninsulin-dependent cells.³⁶ For this reason, the polyol pathway may contribute to these complications, although the mechanism is disputed.

Effects associated with increased polyol activity in peripheral nerve tissue are depletion of myoinositol and decrease in Na⁺, K⁺-adenosine triphosphatase (ATPase) activity.^{37, 38} Another mechanism of damage from sorbitol is through

glycation of proteins. Sorbitol is more likely to exist in the reactive open form of sugars than is glucose. Therefore, in cells with high concentrations of sorbitol, reactions between sugars and proteins are accelerated.¹⁴ In addition, accumulation of the reduced form of nicotinamide adenine dinucleotide may contribute to complications by altering the redox state and allowing a rise in the concentration of diacylglycerol (DAG), and increased activation of some isoforms of protein kinase C (PKC).³⁹ Activation of PKC causes effects such as reduced Na⁺, K⁺-ATPase activity and changes in vascular contractility.^{39, 40} Other abnormalities associated with polyol pathway activity are diminished nitric oxide synthetase and some structural lesions.^{38, 41}

Aldose reductase inhibitors were developed to interfere with accumulation of sorbitol in noninsulin-dependent cells and, it was hoped, with development of complications of diabetes. The agents have some beneficial effects in diabetic neuropathies, including restoration of myoinositol concentrations.^{36, 42} Intracellular concentrations of myoinositol and nerve conduction were improved with administration of either myoinositol or aldose reductase inhibitors in animal models.^{36, 43} A meta-analysis of controlled trials with tolrestat found it to be effective in slowing loss of nerve function in existing peripheral neuropathy.⁴⁴

Vitamins E and C also show promise in preventing complications.^{40, 45} Vitamin E produces a decrease in DAG concentrations in vascular cells, thereby preventing activation of PKC.⁴⁰ This prevents hyperglycemia-induced changes in retinal blood flow in diabetic rats.⁴⁰ Ascorbic acid inhibits the reduction in myoinositol produced by the polyol pathway.⁴⁵

Clinical Trials

Type 1 Diabetes Mellitus

Many trials examined the association between blood glucose concentrations and the onset or progression of chronic complications of diabetes.

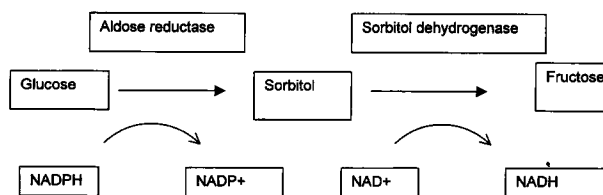


Figure 2. The polyol pathway.

These studies are complicated by a number of factors, including the fact that blood glucose concentrations are not the only determinants of risk. Early clinical trials of glucose control had some additional problems, such as small numbers of subjects in controlled trials and short duration. Until recently, methods of monitoring were not available to achieve and document significant differences in metabolic control between groups.⁴⁶ Subjects using urine glucose monitoring could not safely maintain near normoglycemia, and investigators using occasional blood glucose monitoring had difficulty determining overall glucose control.⁴⁷ However, in the early 1980s, self-monitoring of blood glucose became available.⁴⁸ An additional advance was glycated hemoglobin measurement, which provides an objective and reproducible comparison of integrated differences in glycemic control between groups.⁴⁹ The utility of these two monitoring methods made possible well-controlled comparisons of intensive and conventional therapy.^{6,46}

An early study of glycemic control and complications compared the effects of single (SDI) and multiple (MDI) daily injections of insulin on the progression of retinopathy in 42 subjects with early stages of diabetic retinopathy.⁵⁰ Five of 21 subjects randomized to SDI were changed to two or three injections/day because of poor glucose control, and those randomized to MDI received one to three injections/day. During the 3-year trial, mean fasting blood glucose measurements were not significantly lower in the MDI than SDI group, although significance was reached during the last year of the study (154 ± 15 vs 195 ± 11 mg/dl, $p < 0.05$). Both groups had a significant increase in microaneurysms, but the yearly increase was smaller in the MDI group.⁵⁰ Unfortunately, the large number of subjects moving between treatment groups makes the data difficult to interpret.

Retinopathy and neuropathy were studied in 74 subjects with background retinopathy who were randomized to continue their regular regimen or start intensive therapy.⁵¹ Glycated hemoglobin was lower in intensively treated subjects at 8 and 12 months, but not at 24 months. Creatinine clearance deteriorated in the conventionally treated group and was significantly lower than in the intensive group at 2 years (82.9 ± 26.0 and 99.1 ± 29.6 ml/min, $p < 0.05$). No significant changes in retinopathy were seen in either group. Sensory nerve function improved in subjects receiving intensive therapy and

worsened in those having conventional therapy. The lack of a dramatic difference in glycemic control between groups may have contributed to the absence of effects on retinopathy.

The effects of strict metabolic control on retinopathy and renal function were investigated in a series of studies of continuous subcutaneous infusions of insulin (CSII).⁵²⁻⁵⁷ Thirty-four patients were randomized to either CSII or conventional treatment, which consisted of three injections/day in 13 of 15 patients.^{52,53} Glycated hemoglobin concentration decreased in both groups and was significantly lower in the CSII group after 2 months. After 1 year, deterioration in retinopathy was more frequent in subjects receiving CSII, especially in those with well-regulated blood glucose.⁵³ Urinary albumin excretion showed a trend to decrease by 6 months and glomerular filtration rate (GFR) decreased significantly by 9% ($p < 0.01$) in the CSII group, whereas urinary albumin excretion increased by 56% ($p < 0.01$) and GFR was unchanged in patients who received conventional treatment.

A second study assessed renal function in 36 subjects with elevated urinary albumin excretion randomly assigned to CSII or conventional therapy.^{55,56} A lower mean glycated hemoglobin in CSII-treated subjects was maintained during 2 years of study. The fractional clearance of albumin increased with conventional treatment during the second year and declined in the CSII group, and clinical nephropathy developed in five patients treated conventionally compared with no CSII subjects.⁵⁶ Investigators continued to follow 69 of 70 subjects from both studies. Subjects were allowed to change treatment group after 2 years, and 18 did so. After 3 years, the groups did not differ significantly with respect to glycated hemoglobin concentrations and vision acuity. Direct associations were found between mean glycated hemoglobin and urinary albumin excretion ($p < 0.01$) and change in urinary albumin excretion ($p < 0.01$). Changes in study design cast doubt on the findings. However, these studies showed that although tight glucose control can cause an initial worsening of retinopathy, this effect may be transient.

In 68 subjects, diabetic retinopathy advanced more rapidly in those receiving CSII than in those treated conventionally.⁵⁸ At follow-up in 64 patients after 2 years, 11 receiving CSII and 10 receiving conventional treatment had switched regimens. The CSII group continued to have superior glycemic control based on glycated hemoglobin concentrations; however, the degree

of retinopathy in the two groups was not significantly different.⁵⁹ Despite problems with patients crossing over to the other regimen, these studies support the concept that the initial worsening in established retinopathy seen with strict control may not be evident in the long term.

In 45 patients, CSII was compared with MDI (5 or 6 injections/day) or conventional treatment (2 injections/day).⁶⁰⁻⁶² After 2 years, glycated hemoglobin concentrations were lower in subjects treated with CSII and MDI compared with conventionally treated subjects ($p < 0.01$). Compared with baseline, conventionally treated patients had an increased frequency of microaneurysms and retinal hemorrhages ($p < 0.01$). In addition, they had more microaneurysms and hemorrhages than patients given CSII and MDI ($p < 0.05$). Mean urinary albumin excretion did not change significantly in any group compared with baseline. Despite transient worsening of retinopathy, intensive therapy appeared to be beneficial in delaying progression of complications.

Another trial comparing CSII and conventional therapy in 24 subjects with no or minor background retinopathy and no albuminuria reported no difference between groups with respect to progression of retinopathy after 6 months or urinary albumin excretion after 1 year.⁶³ These data suggest that in patients with minimal retinopathy, intensive therapy may not involve a risk of initial deterioration.

The effects of MDI and conventional treatment on the development of microvascular complications were compared in 96 patients with nonproliferative retinopathy.^{64,65} Glycated hemoglobin concentrations decreased in both groups (MDI $9.5 \pm 0.2\%$ to $7.2 \pm 0.1\%$, $p < 0.001$; conventional treatment 9.4 ± 0.2 to $8.7 \pm 0.1\%$, $p < 0.001$). Retinopathy progressed in both groups, but after 5 and 7 years it was worse in subjects given conventional treatment ($p < 0.05$). In addition, urinary albumin excretion was higher and neuropathy worse in these patients ($p < 0.05$).

The Diabetes Control and Complications Trial (DCCT) studied the effect of intensive therapy in 1441 subjects.⁶ Inclusion of patients relatively soon after diagnosis of diabetes and with no or early complications allowed investigation of the influence of intensive therapy on both primary prevention and early intervention. Inclusion criteria were type 1 diabetes, age 13-39 years, and no evidence of hypertension, hypercholesterolemia, severe diabetic complications, or other medical conditions. Individuals with a 1- to 5-year history of type 1 diabetes mellitus, no signs

of retinopathy, and urinary albumin excretion less than 40 mg/24 hours were included in the primary prevention cohort, and those with a history of type 1 diabetes for 1-15 years, mild to moderate nonproliferative retinopathy, and urinary albumin excretion less than 200 mg/24 hours were the secondary intervention cohort. Subjects were randomized to either intensive or conventional therapy. Those given conventional therapy had one or two insulin injections/day. Those treated with intensive therapy had three or more injections of insulin/day or an insulin pump, and monitored their own blood glucose at least 4 times/day with goals of normal blood glucose and glycated hemoglobin concentrations. Retinopathy, neuropathy, nephropathy, and vascular disease were assessed.

The mean glycated hemoglobin value was significantly different between intensive and conventional treatment groups in both primary and secondary intervention cohorts ($p < 0.001$). The frequency of retinopathy was similar in the intensive and conventional control groups for the first 3 years, but in the long term, intensive therapy reduced the risk of retinopathy in both primary and secondary intervention cohorts. A linear association existed between glycated hemoglobin concentrations and retinopathy in both cohorts. Furthermore, the frequencies of microalbuminuria and neuropathy were reduced in both cohorts. No differences were found between groups in the frequency of any individual vascular event. However, the trend was toward a decrease in combined vascular events with intensive treatment, and intensive therapy decreased the development of hypercholesterolemia. Mortality rates were not significantly different between treatment groups and were lower than expected from population-based mortality studies. However, the frequency of severe hypoglycemia was 3 times higher in intensively treated than in conventionally treated patients ($p < 0.001$). Patients who monitored their own blood glucose gained more weight than their counterparts receiving conventional therapy.

The DCCT established that the risk of development and progression of microvascular complications of diabetes is related to the degree of metabolic control. Intensification of glucose control is associated with deterioration of pre-existent retinopathy, but long-term improvement delays progression of retinopathy. The implications for macrovascular disease are not yet known. Table 1 summarizes these studies.

Table 1. Controlled Clinical Trials of the Effect of Glycemic Control on Chronic Complications in Type 1 Diabetes

Study Population	No. of Pts	Treatment	Duration (yrs)	Outcomes		
				Nephropathy	Retinopathy	Glycated Hemoglobin (%)
Age < 60 yrs, once/day insulin, early retinopathy	42	MDI vs SDI	3	NA	Greater increase microaneurysms SDI vs MDI, 7.2 ± 1.9 vs 1.8 ± 0.7 . ^a	NA
Age < 60 yrs, no renal impairment, significant CV history, or proliferative retinopathy	74	CT ^c vs IT ^d	2	NA	No significant differences between groups.	IT lower than CT after 4 mo, significant at 12 mo, 10.5 ± 1.4 vs 11.4 ± 1.5 . ^a
Age 18–51 yrs, diabetes < 35 yrs, background retinopathy, normal serum creatinine	30	CT ^e vs CSII	1	NA	Improved retinal function in CSII and worse in CT; worse retinal morphology in CSII but not CT.	Decreased in both groups but significantly lower in CSII group.
Age 18–51, diabetes < 35 yrs, background retinopathy, normal serum creatinine	30	CT ^e vs CSII	2	NA	Worse retinal function in CT, ^b CSII unchanged, improved retinal morphology in CSII vs CT. ^b	Mean values lower in CSII vs CT throughout study. ^a
Age 18–50 yrs, diabetes 5–26 yrs, elevated UAE, no active proliferative retinopathy	36	CT ^f vs CSII	1	No differences between groups with respect to UAE or GFR.	No significant differences reported.	Decreased in IT vs baseline, 9.5 to 7.3 ; ^a unchanged in CT, 9.3 to 9.2 .
Age 18–50 yrs, diabetes 5–26 yrs, elevated UAE, no active proliferative retinopathy ^g	36	CT ^f vs CSII	2	Diabetic nephropathy developed more often in CT vs CSII, 5 vs 9 ^b ; UAE increased in CT vs CSII, $+7$ vs -9 ^b .	No significant differences reported.	Decreased in CSII vs baseline, 9.5 to 7.2 . ^h unchanged in CT, 9.3 to 8.6 .
Age 18–51, diabetes < 35 yrs, normal serum creatinine: 1 group with background retinopathy, 1 with elevated UAE	69 ⁱ	CT ^f vs CSII	5 or 8	No patients developed nephropathy, no differences in UAE; independent variables associated with final UAE: HbA _{1c} , ^a and initial UAE. ^h	No difference in progression to proliferative retinopathy or in visual acuity.	Greater decrease in CSII vs CT for both subgroups, 2.0 ± 0.6 vs 0.7 ± 1.2 and 1.8 ± 1.2 vs 0.4 ± 1.3 . ^a
Age 14–60 yrs, weight < 130% IBW, diabetes < 30 yrs, insulin dosage 15–120 U/day for < 2 yrs, mild nonproliferative retinopathy	68	CT ^j vs CSII	2	No differences or changes in patients with normal baseline UAE; for initial elevated UAE, CSII produced decline from baseline but CT did not.	After 1 yr, more deterioration in mean retinopathy level CSII vs CT ⁿ ; after 2 yrs CT worsened and CSII improved. ^h	Mean levels lower in CSII vs CT throughout yr 1, 8.1 ± 0.2 vs 10.0 ± 0.3 ^h and yr 2, 9.0 vs 10.8 . ^a
Age 18–41 yrs, diabetes 5–20 yrs, no or minor background retinopathy	24	CT ^k vs CSII	1	No changes in UAE in either group, decreased GFR CSII, 130 ± 18 – 116 ± 15 ml/min/1.73 m ² , ^b but not CT.	No differences between groups with respect to progression of retinopathy.	Final CSII level decreased from baseline, 8.9 ± 2 to 7.0 ± 1.5 ; ^a unchanged in CT, 9.0 ± 1.9 to 9.1 ± 2 .

Table 1. (continued)

Glucose Concentration (mg/dl)	Outcomes	
	Hypoglycemia	Other
Mean of every third mo fasting glucose concentration higher SDI vs MDI (154 ± 15 vs 195 ± 11). ^b	NA	NA ⁵⁰
NA	No differences between groups; 1 severe episode in each group.	Mean weight unchanged both groups; nerve function improved in IT, worsened CT. ^{b, 51}
Mean concentrations lower CSII vs CT, 112 (range 72–140) vs 176 (range 122–254). ^a	No differences between groups; 6 severe episodes in CSII vs 3 in CT.	NA ^{52, 53}
Mean concentrations lower in CSII vs CT throughout study. ^a	No differences in frequency of blood glucose concentrations < 45; frequency of severe episodes not reported.	NA ⁵
Mean of 1x measurement at end of study lower in IT vs CT, 126 ± 18, 184 ± 36. ^b	No differences in severe episodes CSII vs CT, 3 vs 4.	NA ⁵⁵
Median concentration lower in CSII vs CT, 119 (range 92–162) vs 211 (range 171–311). ^h	5 severe episodes both CSII and CT.	NA ⁵⁶
NA	No significant differences reported.	Systolic blood pressure increased in CT ^b but not CSII. ⁵⁷
Mean plasma concentration during 24-hr profile lower in CSII vs CT, 116.9 ± 5.8 vs 175 ± 8.8. ^h	No differences in severe episodes CSII vs CT, 9 vs 4.	NA ^{58, 59}
Mean daily concentrations lower CSII vs CT, 126 ± 25 vs 166 ± 32. ^a	NA	NA ⁶⁰

Type 2 Diabetes Mellitus

No study of glycemic control in type 2 diabetes mellitus was as well-controlled as the DCCT. However, several trials showed a relationship between glycemia and complications in these patients.

The University Group Diabetes Program was an early attempt to study the effects of various treatment options in type 2 disease.⁶⁶ This was a randomized, prospective comparison of cardiovascular and microvascular outcomes achieved with five treatment regimens in 1027 patients: diet alone, diet plus fixed-dose insulin, diet plus variable-dose insulin, diet plus tolbutamide, and diet plus phenformin. The fixed-dose regimen was no more than 20 U intermediate-acting insulin every morning. The variable dose was adjusted with the goal of periodic fasting glucose concentrations below 130 mg/dl. The study was begun in 1961, before evidence of contributing risk factors to cardiovascular disease and availability of glycosylated hemoglobin measurements or self-monitoring of blood glucose; the phenformin group was added later. The tolbutamide and phenformin arms were stopped early because these patients had an increase in overall and cardiovascular mortality. However, the other arms continued for 6 years. Improved glucose control was not associated with insulin, phenformin, or tolbutamide over the 11 years of follow-up. Phenformin and tolbutamide, but not insulin, were associated with increased cardiovascular deaths. The results remain controversial and have been subjected to several post hoc analyses.^{67–69} It is still not known whether choice of agent affects the risk of complications independent of glycemic control.

In a prospective study, 1054 elderly (age 65–74 yrs at baseline) patients were assessed for weight, height, blood pressure, evaluation of coronary heart disease, glucose tolerance, and glycosylated hemoglobin at baseline and after 2.7–5.2 years.⁴ At baseline, 17.9% of men and 19.0% of women had impaired glucose tolerance, 7.0% and 7.1% had newly diagnosed type 2 diabetes mellitus, and 8.7% and 11.6% had previously diagnosed type 2 diabetes. In subjects with diabetes, both glycosylated hemoglobin and duration of disease were strongly correlated with risk of myocardial infarction and other vascular events. Elevated glycosylated hemoglobin was a stronger predictor than duration of disease (short duration and glycosylated hemoglobin ≥ 7.0% were worse than long duration and glycosylated hemoglobin < 7.0%). Other factors, such as current smoking, systolic

Table 1. Controlled Clinical Trials of the Effect of Glycemic Control on Chronic Complications in Type 1 Diabetes (cont.)

Study Population	No. of Pts	Treatment	Duration (yrs)	Outcomes		
				Nephropathy	Retinopathy	Glycated Hemoglobin (%)
Age 18–45 yrs, diabetes 7–30 yrs, no nephropathy, hypertension, or proliferative retinopathy	45	CSII vs MDI ^l vs CT ^m	1, 2	No significant changes or differences between groups in UAE.	Worsening retinopathy in CSII at 3 and 6 mo but not 1 or 2 yrs; MDI had no changes throughout study; CT worse at 1 and 2 yrs. ^c	Greater decrease from baseline in CSII vs MDI and CT, 10.1 ± 0.4 to 8.7 ± 0.3, 9.4 ± 0.4 to 9.1 ± 0.4, 9.5 ± 0.4 to 10.2 ± 0.5. ^a
Nonproliferative retinopathy, normal serum creatinine, unsatisfactory glycemic control	95	MDI ⁿ vs CT ^f	7.5	Fewer patients developed nephropathy MDI vs CT, 1 vs 9. ^b	Fewer patients developed serious retinopathy in MDI vs CT, 27% vs 52%. ^d	Mean level lower in MDI vs CT, 7.1 ± 0.7 vs 8.5 ± 0.7. ^a
Age 13–39 yrs, no or early microvascular complications, no hypertension or hypercholesterolemia	1441	CT ^f vs IT ^o	6.5	Decreased risk microalbuminuria in IT vs CT both cohorts, primary 34%, ^b secondary 43%. ^a	IT vs CT decreased risk of developing (76%) ^c or progressing (54%). ⁿ	IT lower than CT ^h throughout study.

MDI = multiple daily injections of insulin; SDI = single daily injection of insulin; CV = cardiovascular disease; CT = conventional therapy; IT = intensive therapy; CSII = continuous subcutaneous infusion of insulin; UAE = urinary albumin excretion; GFR = glomerular filtration rate; HbA_{1c} = glycated hemoglobin; IBW = ideal body weight; NCV = nerve conduction velocity; NA = not applicable.

^ap<0.01.

^bp<0.05.

^cConventional treatment consisted of therapy used before the study; 63% were receiving once/day regimens.

^dIntensive therapy consisted of Ultralente plus short-acting insulin with meals.

^eConventional treatment consisted of two daily injections for 93.3% patients

^fConventional therapy consisted of two to three daily injections of short- ± intermediate-acting insulin.

^gThe same subjects are reported in references 55 and 56.

^hp<0.001.

ⁱReference 57 includes subjects who were enrolled but may not have completed studies in references 52, 53, 55, and 56.

^jConventional therapy consisted of one to three daily injection of short- ± intermediate-acting insulins.

^kConventional therapy consisted of twice daily injections of insulin.

^lMultiple daily injections consisted of short-acting insulin before meals and intermediate-acting insulin at bedtime.

^mConventional therapy consisted of twice/day injections of short- ± intermediate-acting insulin.

ⁿMultiple daily injections consisted of three or more daily injections in 82%.

^oIntensive therapy consisted of three or more injections of insulin daily with self-monitoring of blood glucose.

blood pressure, and low high-density lipoprotein, did not predict coronary heart disease events.

A prospective study compared an intensive insulin regimen with conventional insulin therapy in 110 patients who had previously been treated with one or two daily injections of insulin.⁷⁰ Patients with hypertension were excluded. The study design resembled that of the DCCT, with primary prevention (no retinopathy, urinary albumin excretion < 30 mg/24 hrs) and secondary intervention (simple retinopathy, urinary albumin excretion < 300 mg/24 hrs) cohorts. Those randomized to

conventional therapy received one or two injections/day of intermediate-acting insulin with the goals of preventing symptoms of hypoglycemia and hyperglycemia and maintaining fasting blood glucose below 140 mg/dl. The intensively treated group received short-acting insulin with each meal and intermediate-acting insulin at bedtime. A significant improvement in glycemic control, achieved with intensive therapy, was associated with a decreased risk of microvascular complications. However, exclusion of patients with hypertension and the fact that few subjects were obese led to questions about

Table 1. (continued)

Glucose Concentration (mg/dl)	Outcomes	
	Hypoglycemia	Other
Greater decrease from baseline in mean glucose concentration CSII and MDI vs CT, 160 ± 13 to 95.4 ± 5.4, 162 ± 14 to 115 ± 5.4, 142 ± 13 to 142 ± 9. ^a	Larger increase from baseline in number of blood glucose < 45 in CSII than MDI, CT ^b ; fewer episodes of hypoglycemic coma CSII than MDI, CT (2 vs 14 vs 13.) ^b	NA ⁶¹⁻⁶³
NA	Episodes of severe hypoglycemia; in MDI and CT, 1.1 vs 0.4/patient-yr.	No differences between groups in development of peripheral neuropathy, less deterioration in NCV, MDI vs CT. ^{a, 64, 65}
Mean blood concentration lower in IT vs CT, 155 ± 30 vs 231 ± 55. ^h	Severe episodes more common in IT vs CT, 62/100 vs 19/100 patient-yrs. ^h	41% decrease in total macrovascular events; IT gained 4.6 kg more than CT. ⁶

applicability of results to the usual population with type 2 diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS) randomized obese patients to diet alone or diet plus insulin, chlorpropamide, glyburide, or metformin. Nonobese patients had the same options with the exception of metformin. Long-term outcome data are not yet available, although data on glycemic control have been published. The results of this study may help determine if drug therapy has any effect on the development of chronic complications.^{71, 72} Table 2 summarizes studies in type 2 disease.

A feasibility study was conducted for a large, prospective trial of intensive versus conventional insulin therapy in patients with poor control despite treatment with oral agents or standard insulin therapy.^{73, 74} The study would address whether intensive therapy is of benefit in people who failed other drug therapies, rather than indicating whether intensive therapy from the time of diagnosis is beneficial.

Even if improved glucose control reduces the risk of chronic complications in type 2 diabetes, drugs may differ in their benefit. Epidemiologic data linked hyperinsulinemia in nondiabetics with an increased rate of atherosclerosis.⁷⁵ However, it may be that hyperinsulinemia is a

marker for, rather than a cause of, cardiovascular risks.⁷⁶ Moreover, clinical trials did not find an association between insulin dosages and cardiovascular events. In addition, it was theorized that sulfonylureas could cause cardiovascular toxicity due to closure of ATP-sensitive potassium channels; if true, this may vary among members of the class.^{77, 78} Other agents, such as thiazolidinediones and biguanides, have potentially beneficial effects on macrovascular risks such as decreasing insulin resistance and improving the lipid profile.^{79, 80} The final results of the UKPDS should clarify the contribution of treatment to risk of complications.

Special Patient Populations

The American Diabetes Association (ADA) and others identified patients for whom intensive therapy may not be indicated.^{6, 81-83} Intensive therapy should be implemented with great caution in patients who experience frequent episodes of severe hypoglycemia or have hypoglycemic unawareness.⁴ In addition, it is contraindicated in patients with unusual potential to suffer harm from hypoglycemia.^{6, 72} Those who have had diabetes for 20 or more years after adolescence without complications are unlikely to develop complications ever and may not benefit from intensive therapy.⁸¹ Because the primary benefits in the DCCT were decreased occurrence and progression of retinopathy and renal disease, having these disorders in advanced stages eliminates much of the potential benefit of intensive therapy and still carries the risks. Therefore, the ADA does not recommend such treatment for patients with end-stage renal disease or severe retinopathy.⁸¹

The youngest subject enrolled in the DCCT was 13 years of age, and the benefits of intensive therapy in children have not been well defined.⁶ Children may have both a reduced possibility of benefiting and an increased risk of harm.^{8, 82, 84} Epidemiologic data suggest that preadolescent children may be protected from the microvascular damage of hyperglycemia.^{82, 85, 86} Hypoglycemia in children could impair normal brain development, which is not complete until age 7 years. For these reasons, intensive therapy is contraindicated in patients under age 2 years, should be prescribed only with extreme caution in those age 2-7, and possibly not begun until after age 13.⁸¹

Conclusion

The DCCT and other trials of intensive therapy

Table 2. Controlled Clinical Trials of the Effect of Glycemic Control on Chronic Complications in Type 2 Diabetes

Study Population	No. of Pts	Study Design/Treatments	Duration (yrs)	Outcomes			
				Retinopathy	Nephropathy	Glycated Hemoglobin	Glucose Concentration (mg/dl)
Newly diagnosed, not requiring insulin	1027	Diet, fixed-dose T, fixed-dose I, variable-dose I, fixed-dose P	6 ^a	NA	NA	NA	Fasting and 1 hr after load higher in D and fixed I vs variable I throughout study.
Insulin-treated, no or early microvascular complications, no hypertension	110	IT, CT	6	Fewer in IT vs CT developed (7.7%, 32%) or progressed (19.2%, 44%) ^b at 6 yrs.	Fewer in IT vs CT developed (7.7%, 28%) or progressed (11.5%, 32%) ^b at 6 yrs.	Lower in IT vs CT, 7.1 ± 1.1 vs 9.4 ± 1.5% ^c throughout study.	Fasting (126 ± 36, 164 ± 50) and mean (157 ± 34, 221 ± 45) lower in IT vs CT ^d throughout study.
Newly diagnosed	5102	Nonobese: CT = diet; IT = C, G, or I; obese CT = diet IT = C, G, I, or M	9	NA	NA	Nonobese: lower in IT vs CT, 6.7% vs 7.5% ^d ; obese: lower in IT vs CT, 7% vs 7.7%.	Nonobese: mean fasting lower in IT vs CT, 117 vs 133.4 ^d ; obese: mean fasting lower in IT vs CT, 144 vs 167.4. ^d

T = tolbutamide; I = insulin; P = phenformin; M = metformin; D = diet alone; IT = intensive therapy; CT = conventional therapy; C = chlorpropamide; G = glyburide; NA = not applicable.

^aTolbutamide and phenformin arms stopped early.

^bp<0.05.

^cp<0.001.

^dp<00001.

indicated that achieving optimum blood glucose concentrations is a critical part of the treatment of diabetes mellitus. Barriers to widespread implementation of intensive therapy include unfamiliarity of health care providers and patients with it, and financial concerns.

The DCCT used MDI or an insulin pump, self-monitoring of blood glucose at least 4 times/day with adjustment of insulin dosage based on the results, and careful attention to diet and exercise. Patient care was coordinated by teams of specialists. In contrast, most people with diabetes receive care from a primary care physician. Even lacking the support necessary to implement intensive care, however, improvement in glycemic control is indicated. Glycated hemoglobin concentrations in the DCCT were lower in patients receiving intensive therapy than in those receiving conventional therapy, but they were still not within normal limits. Thus, patients can be reassured that improvement in glycemic control is beneficial despite failure to achieve normal values.

The cost of treating the 1441 subjects in the DCCT for a mean of 6.5 years was \$165 million, or over \$17 thousand/patient/year; some of this cost was probably dictated by research rather than clinical needs. It is difficult to assess what

the cost would be if intensive therapy were implemented in all patients in whom it is indicated. Preliminary cost analysis is being conducted to determine if the possible savings from decreased complications will more than offset the cost of therapy.

Intensive therapy should be pursued in all patients for whom it is indicated. This does not preclude treatments known to decrease the risk of complications, such as hypertension and hyperlipidemia, and to delay progression of diabetic nephropathy. In the future, treatment may also include agents to interfere with the harmful effects of hyperglycemia.

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6. The Diabetes Control and Complications Trial Research

Table 2. (continued)

Outcomes	
Hypoglycemia	Other
More changes in regimen due to hypoglycemia in variable insulin vs fixed-dose or placebo (40%, 15%, 0%).	Increased CV mortality with T and P, no differences in mortality between other groups. ⁶⁹
One or more mild reactions: IT 6 patients, CT 4 patients; no severe reactions.	NA ⁷⁰
Patients with major events: Overall: D = 0.03%, C/G = 0.7%, I = 2.3%; Obese: D = 0.1%, M = 0.3%.	Mean increase in body weight: Overall: D = 3 kg, C/G = 5 kg, I = 7kg; Obese: D = 1 kg, C/G = 5 kg, M = 1 kg. ^{71,72}

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