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Targets for glycemic control: What is the evidence?

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A causal relationship between high glucose levels and the chronic complications of diabetes was postulated long before the results of recent studies illustrating the benefits of intensive glycemic control. The presence of microvascular complications is unique to diabetes mellitus and accounts for a significant degree of morbidity due to loss of vision,[1] renal failure,[2] and amputation.[3] Moreover, diabetes is associated with a heightened risk of cardiovascular disease, contributing to higher mortality rates in the diabetic as compared to the non-diabetic population.[4] There is now compelling evidence from randomized controlled trials that the long-term complications of diabetes can be reduced by tight glycemic control. This has led the Canadian Diabetes Association (CDA) and other organizations to recommend stricter targets for therapy.[5] The 1998 CDA guidelines suggest that, for the majority of patients, (Table 1) these levels be maintained:

- **HbA_{1c} to within 115% of the upper limit of normal (<7% in most labs)**
- **pre-prandial levels between 4 and 7 mmol/L, and**
- **2-hour post-prandial levels between 5 and 11 mmol/L**

In recent years, there has been an emerging body of evidence regarding pre- and post-prandial glycemia and its role in the development of chronic complications of diabetes. The CDA has started a careful review of the literature to re-evaluate the targets of glycemic control and other aspects of diabetes management and a revised set of guidelines is planned for release in 2003. In this issue of *Endocrinology Rounds,* the evidence surrounding glycemic control and its effect on diabetic complications will be reviewed. Where randomized clinical trials are lacking, attention will focus on prospective epidemiological data, with the purpose of building a framework for developing targets of glycemic control.

The effect of glycemic control on diabetic complications

Type 1 diabetes mellitus

The Diabetes Control and Complications Trial (DCCT) was a large, multicentre, randomized trial that enrolled 1441 patients with type 1 diabetes in 29 centres throughout North America.[6] The DCCT evaluated the effect of an intensive insulin regimen aimed at achieving glucose levels as close to the normal range as possible versus a conventional insulin regimen. For those in the intensive treatment (IT) arm, an insulin regimen consisting of multiple daily injections (MDI) or a subcutaneous insulin infusion was implemented to achieve an HbA_{1c} <6.05% and pre-meal glucose levels between 3.9 and 6.7 mmol/L. This intensive program of therapy was coupled with frequent self-monitoring, insulin dose adjustment, and close contact with a diabetes health team. In contrast, those on conventional therapy (CT) received one or two injections of insulin per day with the aim of avoiding excessive symptoms of hyper- or hypoglycemia, and were followed less frequently.

During the DCCT, intensive therapy resulted in a significantly lower mean HbA_{1c} level compared with conventionally-treated patients (7.2% vs. 9.0%, $P<0.001$) and this difference was maintained throughout the course of the study. Intensive therapy dramatically reduced the risk of developing new or progressive microvascular complications. Retinopathy was reduced by up to 76% (95% confidence interval (CI), 62% - 85%), microalbuminuria by 39% (95% CI, 21% - 52%), overt proteinuria by 54% (95% CI, 19% - 74%), and clinical neuropathy by 60% (95% CI, 38% - 74%). However, in addition to this benefit, IT was associated with a 2- to 3-fold increase in the risk of severe hypoglycemia.

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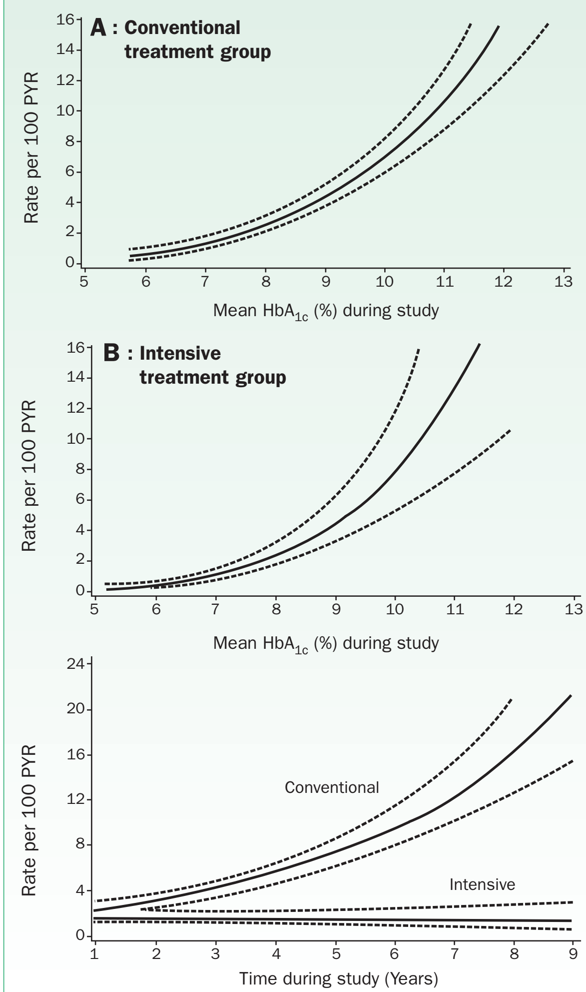
Table 1: Targets for glycemic control: The 1998 Canadian Diabetes Guidelines[5]

	Ideal	Optimal	Suboptimal	inadequate
HbA_{1C}*	≤100	≤115	116-140	>140
Fasting/pre-meal BG (mmol/L)	3.8-6.1	4-7	7.1-10	>10
Post-meal BG (mmol/L)	4.47-7.0	5-11	11.1-14	>14

* % of upper limit of assay

Figure 1: Relationship between a sustained progression in retinopathy and the updated mean HbA_{1c} (%) achieved during the DCCT[7]



A secondary analysis of the DCCT data revealed a continuous relationship between HbA_{1c} and microvascular disease both before, and after, adjustment for other confounders.[7] There was no apparent threshold for the beneficial effect of lowering HbA_{1c} on the progression of retinopathy. In both treatment groups, a 10% reduction in HbA_{1c} (eg, from 8% to 7.2%) was associated with a 40% to 50% lower risk of progression (Figure 1). Thus, the lowest risk occurred in patients who achieved a mean HbA_{1c} of < 6%, however, only a few were able to achieve this degree of glycemic control. Baseline HbA_{1c} and disease duration were also important predictors of retinopathy progression, suggesting that total glycemic exposure contributes to the development of microvascular disease. During the study, the change in risk over time also depended on how glycemic control was attained. CT patients had consistently higher rates of microvascular endpoints than the IT patients who achieved the same HbA_{1c}. Hence, it is possible that greater fluctuations in glucose levels throughout the day play an independent role in the development of complications.

A more recent analysis of the DCCT data published in 2001, found a similar relationship between mean blood glucose levels from 7-point glucose profiles and progression of retinopathy.[8] On a quarterly basis, participants on IT did more frequent monitoring, performing a 7-point glucose profile of both pre- and post-prandial levels at home. There was a progressive increase in the risk of retinopathy when mean blood glucose (BG) levels were > 8.3 mmol/L. However, too few participants achieved levels lower than this to extend the regression line below this point, thus the authors were unable to replicate the continuous relationship between average glucose levels and complications that had been illustrated previously.

The DCCT was the first large-scale randomized controlled trial (RCT) to demonstrate the benefit of glucose control on complications of type 1 diabetes. Earlier randomized trials comparing IT to CT insulin regimens included too few patients to be conclusive.[9-18] One exception was the Stockholm Diabetes Intervention study[19] that reported a decrease in the risk of proliferative retinopathy (27% vs. 52%, $P = 0.01$) and nephropathy (18% vs. 2%, $P = 0.01$), despite a smaller sample size (n = 96) and a large number of crossovers between the CT and IT groups. A meta-analysis of 16 individual studies revealed an overall reduction in the risk of retinopathy progression, relative risk (RR): 0.49 (0.28-0.85) and nephropathy, RR: 0.34 (0.2-0.58) after only 2 years of intensive insulin therapy.[20]

To date, no studies have specifically examined the effect of IT on cardiovascular endpoints in patients with type 1 diabetes. In the DCCT, IT was associated with a 42% lower likelihood of a first major macrovascular event (0.84 vs. 0.49 per 100 person-years, $P = 0.082$), including 78% fewer coronary artery disease events (0.29 vs. 0.06 per 100 person-years, $P = 0.065$); however, these findings were not statistically significant.[6] A meta-analysis that integrated the results of 6 studies (including the DCCT), discovered a significant reduction in the risk of a first macrovascular event in patients treated with IT compared to CT (odds ratio (OR) 0.55 (0.35-0.88), $P = 0.015$).[21] Improved glycemic control may have a beneficial effect on serum lipids and endothelial function in this population.[22,23]

Type 2 diabetes mellitus

Two randomized controlled trials have evaluated the effect of IT on the complications associated with type 2 diabetes.

The first, a small Japanese study (Kumamoto trial), randomized 110 participants with type 2 diabetes mellitus treated with insulin, to receive multiple injections (3 to 4 per day) versus CT with 1 or 2 injections per day.[24] The aim of IT was to achieve an HbA_{1c} of <7%, fasting glucose of <7.8 mmol/L, and post-prandial levels of ≤11.1 mmol/L. The study was successful in attaining these goals; IT resulted in a median HbA_{1c} of 7.1% compared with 9.4% in the CT group and a lower risk of microvascular complications. The cumulative incidence of retinopathy was lower among participants on IT (7.7% vs. 32%, $P=0.039$), as was the incidence of nephropathy (7.7% vs. 28%, $P=0.032$). Abnormalities on neurological testing were also less common among those on IT. In a secondary analysis, the risk of either retinopathy or nephropathy rose with increasing HbA_{1c} levels >6.5% - 7%. None of the participants who achieved an HbA_{1c} of <6.5% showed progression; however, this finding was based on very few events and not adjusted for potential confounders.

The United Kingdom Prospective Diabetes Study (UKPDS) was a large, randomized, controlled trial that recruited over 4000 patients with newly diagnosed type 2 diabetes melitus who had a fasting glucose levels >6.0 mmol/L on at least two occasions.[25,26] The UKPDS was designed to compare the effect of an intensive versus a conventional treatment policy on microvascular, as well as macrovascular complications. In the main trial, participants in the IT group received a sulphonylurea or an insulin-based regimen that was titrated to achieve a fasting BG <6 mmol/L, and for those on insulin, pre-meal levels between 4 and 7 mmol/L. In contrast, CT patients were treated with diet therapy alone, unless they developed symptoms or a fasting glucose level >15 mmol/L. The IT group achieved a lower HbA_{1c} than the CT patients (median 7% vs. 7.9%). Glycemic control deteriorated throughout the course of the study, however, the difference between the 2 treatment groups remained significant. IT resulted in a significantly lower risk of any diabetes-related endpoint (RR reduction (RRR): 12%; 95% CI, 1%-21%), microvascular events (RRR: 25%; 95% CI, 7%-44%), and retinal photocoagulation (RRR: 29%; 95% CI, 4%-67%). There was also a trend towards lower rates of myocardial infarction, although this did not reach statistical significance (RRR: 16%, $P=0.052$).

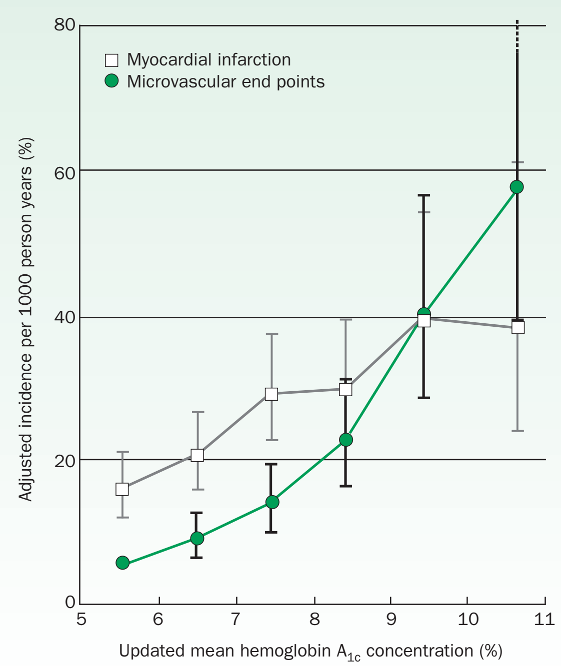
Again, a direct relationship was observed between the mean updated HbA_{1c} level achieved during the trial and clinical outcomes with no obvious threshold of benefit.[27] Each 1% (absolute) reduction in mean updated, HbA_{1c} concentration was associated with a 37% decline in the risk of microvascular endpoints ($P<0.0001$), a 14% lower rate of myocardial infarction (MI; $P<0.0001$), and fewer diabetes-related deaths or mortality from any cause ($P<0.0001$; Figure 2). Glycemic control remained an important predictor of most diabetes-related endpoints after adjustment for age, sex, ethnicity, blood pressure, smoking, serum lipids, albuminuria, and treatment allocation, with the exception of stroke and heart failure. From their analysis, mean updated HbA_{1c} levels >7% were associated with a significantly increased risk for most endpoints compared to levels <6%. Although there appeared to be a relative benefit to lowering HbA_{1c} levels from 7% to 6%, the absolute benefit appeared to be small. Additional data found that a mean updated HbA_{1c} in the 6.2% to 7.4% range (representing the middle tertile) was associated with a significantly higher rate of progression in retinopathy compared to levels <6.2%.[28] This was particularly evident for individuals who had background retinopathy. In another analysis, participants with baseline HbA_{1c} concentrations >7.6% had a 50% higher risk of MI (RR: 1.5; 95% CI, 1.2-1.9), while those with levels over 6.3% had a significantly increased risk of angina (RR: 1.5; 95% CI, 1.1-2.0).[29]

The Munich General Practitioner Project was a prospective cohort study that evaluated the relationship between baseline HbA_{1c} and subsequent coronary heart disease mortality over a 10-year period.[30] The study population was randomly selected from a representative sample in primary care practices of middle-aged individuals with type 2 diabetes. Baseline HbA_{1c} levels of ≥6.9% were associated with a >2-fold higher mortality rate, regardless of baseline cardiovascular status. HbA_{1c} levels in the highest tertile (over 8.8%) were not associated with a further elevation in risk, however, they did not examine HbA_{1c} as a continuous risk factor. The effect of glycemic control was independent of other prognostic factors.

The relationship between fasting/pre-meal glucose levels and diabetes complications

Self-monitoring of blood glucose levels is an important tool that can be used to adjust therapy for individuals with

Figure 2: Incidence rates for myocardial infarction and microvascular complications by category of updated mean HbA_{1c}[27]



either type 1 or type 2 diabetes. In both the DCCT and UKPDS, participants treated with an IT regimen used 4-7 mmol/L as their pre-meal target range to adjust therapy.[6,25] During the DCCT, a mean glucose level of 8.6 mmol/L was associated with a mean pre-prandial blood glucose that was somewhat higher than the threshold (7.7 mmol/L), suggesting that for patients with type 1 diabetes, these targets may be difficult to achieve. In contrast, in the UKPDS IT group, therapy was titrated with the aim of lowering fasting glucose to <6 mmol/L and this resulted in a reduced risk of microvascular complications. However, despite ongoing vigilance, HbA_{1c} levels continued to rise during the course of the trial, suggesting that targeting fasting glucose levels alone may not be sufficient to achieve good glycemic control. Furthermore, several studies have demonstrated that a single, fasting, plasma glucose can not reliably predict HbA_{1c} measurements, and that glucose levels obtained at other times of the day may be more meaningful.[31-33]

Exactly how low fasting and pre-meal levels should be maintained is still a matter of debate. Data from the Kumamoto study found that fasting BG levels over 6.1-6.7 mmol/L were associated with an increased risk of microvascular complications.[24] Data from other prospective studies highlight the role of fasting glucose in the development of macrovascular events. Coutinho et al published a meta-regression analysis of data from 20 studies, involving 95,783 people, evaluating the effect of fasting glucose on the incidence of coronary heart disease events.[34] To examine the impact of glucose levels in the non-diabetic range, they only reviewed studies that included persons without diabetes. From their analysis, a fasting glucose of ≥ 6.1 mmol/L was associated with increased risk of CHD events compared to a level < 4.2 mmol/L (RR 1.33; 95% CI, 1.06-1.67) regardless of diabetes status. Removing the top quintile of glucose levels did not change the results substantially. Furthermore, there was a continuous association between glucose and cardiovascular events, with the risk rising even when levels were within the normal, nondiabetic range.

The relationship between post-meal glucose levels and diabetes complications

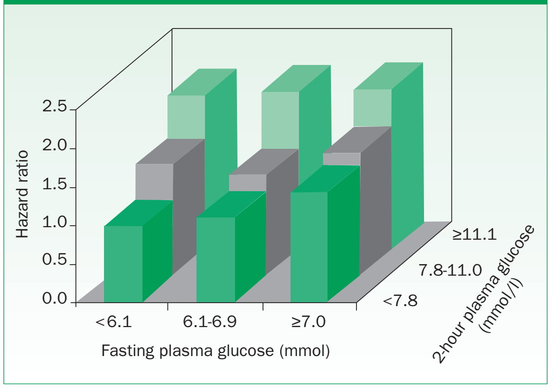
Recent studies have provided new insight into the relationship between post-prandial glycemia and macrovascular disease. Most of the evidence in this area comes from prospective studies where participants underwent screening with an oral glucose tolerance test (OGTT) at baseline. A number of studies have found post-challenge glucose to be a powerful and independent predictor of cardiovascular risk in individuals with and without diabetes.

One of the largest studies to examine this relationship is the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study that aggregated data from 13 prospective cohort studies (n = 25,364).[35] Overall, a 2-hour post-challenge glucose between 7.8 and 11.0 mmol/L was associated with a 50% higher mortality rate (RR: 1.50; 95% CI, 1.33-1.69), while levels ≥ 11.1 mmol/L were associated with 2-fold greater mortality (RR: 2.13; 95% CI, 1.79-2.52) than those with normal glucose tolerance (Figure 3). This trend was observed among individuals who had diabetes based on a fasting glucose > 7.0 mmol/L, as well as those who had fasting levels in the nondiabetic range. In a similar analysis, post-challenge glucose remained an independent predictor of cardiovascular mortality after adjusting for other risk factors, and for fasting glucose. In contrast, fasting glucose was no longer a significant predictor after controlling for post-prandial elevations.[36]

The Diabetes Intervention Study was a prospective, cohort study that followed newly diagnosed patients with type 2 diabetes (n = 1139) for the development of myocardial infarction (MI) and death over an average of 12 years.[37] A number of measures were obtained at baseline, including a post-prandial glucose (PPG) obtained 1 hour after the participant's usual breakfast. In a case-control analysis, PPG levels were somewhat higher in participants who died compared to survivors (8.9 vs. 8.4 mmol/L, $P < 0.01$). Furthermore, when they examined the relationship across categories of PPG, there appeared to be a significant trend towards a higher incidence of MI and mortality with increasing 1-hour PPG levels. The lowest risk of MI or death was associated with a 1-hour PPG of 8 mmol/L or less; PPG levels >10 mmol/L were associated with the highest risk, and levels of 8-10 mmol/L had an intermediate risk ($P < 0.05$).

Few studies have examined the risk of microvascular endpoints in relation to post-prandial glycemia. In the Kumamoto study, the risk of microvascular complications also started to rise with a 2-hour PPG level > 10 mmol/L.[24] Unfortunately, a similar analysis of DCCT data is not available. Participants in the DCCT did not routinely adjust their insulin therapy on the basis of post-prandial readings. However, based on their quarterly 7-point glucose measurements, they also sought to achieve a 90-min PPG level < 10 mmol/L. Among those on IT, a mean HbA_{1c} of 7.2% was associated with a mean PPG of 9.4 mmol/L. A recent analysis reviewed the relationship between mean pre- or post-prandial glucose levels and HbA_{1c} achieved during the DCCT.[38] Correlation coefficients were somewhat (albeit marginally) greater in the post-prandial period, with the weakest association occurring between fasting glucose and HbA_{1c} ($r = 0.69$), and the strongest association in the 90-minute post-lunch ($r = 0.77$) and post-

Figure 3: The relationship between all-cause mortality and 2-hour plasma glucose by category of fasting glucose[35]



Adapted from DECODE Study Group[35]

dinner (r = 0.78) period. Other studies also suggest that PPG levels may be a better predictor of HbA_{1c} than pre-prandial levels. In a small, randomized study, women with gestational diabetes who adjusted their insulin therapy based on 1-hour PPG levels rather than pre-prandial readings experienced a greater reduction in HbA_{1c}.[39] Cross-sectional data suggest that a single plasma 2-hour PPG > 8.9 is neither sensitive, nor specific, for predicting high HbA_{1c} levels, although post-lunch levels > 11.5 were specific for poor control.[32,33] Thus, monitoring on a regular basis and adjusting therapy based on the average glucose levels achieved in the pre- or post-prandial period, rather than single readings, may be more highly correlated with HbA_{1c}, as it was in the DCCT.

Conclusions

While there is clearly evidence that lowering HbA_{1c} through IT will lead to improved outcomes, deciding on specific targets of glycemic control is a matter of some debate. Each of the 3 main randomized studies achieved HbA_{1c} levels of approximately 7% in their IT group and demonstrated a clear rise in the risk of complications with levels exceeding this threshold. Lowering HbA_{1c} levels to 6% is expected to further reduce the risk of complications. However, the DCCT analysis demonstrated a curvilinear relationship between HbA_{1c} and microvascular outcomes, thus, the magnitude of risk reduction associated with lowering levels from 7% to 6% was small, although the relative gains may be high. Even if the true relationship is linear, as suggested by the UKPDS, as the baseline risk falls, so will the absolute benefit achieved by further reductions. Thus, the benefit of attaining normoglycemia needs to be weighed against the risk of hypoglycemia. Optimal glucose levels appear to be those that are as close to normal as possible, as long as they can be achieved safely.

Non-fasting glucose measurements, particularly those taken in the post-prandial period, may be a better predictor of HbA_{1c}. Moreover, a number of prospective studies have highlighted the importance of post-prandial glycemia in the development of cardiovascular disease. The evidence suggests that post-meal glucose levels < 8 mmol/L confer the lowest risk of cardiovascular disease and that levels > 10 mmol/L can substantially increase this risk. To date, there are no studies that have demonstrated a significant reduction in cardiovascular events with intensive therapy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a large multicentred study, which is now underway across the US and Canada.[40] The ACCORD trial is powered to evaluate the effect of very tight glycemic control (HbA_{1c} < 6%) compared to conventional control (HbA_{1c} ~ 7.5%) on cardiovascular endpoints in patients with type 2 diabetes. Until this landmark study is completed, thresholds for therapy will be largely based on epidemiological studies. Based on current data, targets of therapy should include both pre- and post-prandial thresholds, in order to optimize treatment aimed at reducing the level of glycemia and its associated risk.

References

1. Klein R, Klein BEK. Vision disorders in diabetes. In: National Diabetes Data Group, ed. *Diabetes in America*. 2nd ed. Washington, DC: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995:293-338.
2. Nelson RG, Knowler WC, Pettitt DJ, Bennett PH. Kidney diseases in diabetes. In: National Diabetes Data Group, ed. *Diabetes in America*. 2nd ed. Washington, DC: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995:349-400.
3. Bild DE, Selby JV, Sinock P, Browner WS, Braveman P, Showstack JA. Lower-extremity amputation in people with diabetes: epidemiology and prevention. *Diabetes Care* 1989;12: 24-31.
4. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971-1993. *Diabetes Care* 1998;21:1138-1145.
5. Meltzer S, Leiter L, Daneman D, et al. 1998 Clinical Practice Guidelines for the management of diabetes in Canada. Canadian Diabetes Association. *CMAJ* 1998;159 (Suppl 8):S1-S29.
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986.
7. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 1995;44:968-983.
8. Service FJ, O'Brien PC. The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. *Diabetologia* 2001;44:1215-1220.
9. Eschwege E, Job D, Guyot-Argenton C, Aubry JP, Tchobroutsky G. Delayed progression of diabetic retinopathy by divided insulin administration: a further follow-up. *Diabetologia* 1979;16:13-15.
10. Deckert T, Lauritzen T, Parving HH, Christiansen JS, Steno Study Group. Effect of two years of strict metabolic functions in long-term insulin-dependent diabetes. *Diab Nephropathy* 1984;3:6-10.

11. Olsen T, Richelsen B, Ehlers N, Beck-Nielsen H. Diabetic retinopathy after 3 years' treatment with continuous subcutaneous insulin infusion (CSII). *Acta Ophthalmol* 1987;65:185-189.
12. Verillo A, de Teresa A, Martino C, Verillo L, di Chiara G. Long-term correction of hyperglycemia and progression of retinopathy in insulin dependent diabetes: a five-year randomized prospective study. *Diabetes Res* 1988;8:76.
13. Brinchmann-Hansen O, Dahl-Jørgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. *Arch Ophthalmol* 1988;106:1242-1246.
14. Lauritzen T, Larsen KF, Larsen HW, Deckert T, Steno Study Group. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes* 1985;34 (Suppl 3):74-79.
15. The Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. *N Engl J Med* 1984; 311:365-372.
16. Beck-Nielsen H, Richelsen B, Mogensen CE. Effect of insulin pump treatment for one year on renal function and retinal morphology in patients with IDDM. *Diabetes Care* 1985;8:585-589.
17. Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. *Lancet* 1985;ii:1300-1304.
18. Christensen CK, Christiansen JS, Schmitz A, Christensen T, Hermansen K, Morgensen CE. Effect of continuous subcutaneous insulin infusion on kidney function and size in IDDM patients: a 2-year controlled study. *J Diabet Complications* 1987;1:91-95.
19. Reichard P, Nilsson B-Y, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304-309.
20. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. *Lancet* 1993;341:1306-1309.
21. Lawson ML, Gerstein HC, Tsui E, Zinman B. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. A systematic review and meta-analysis. *Diabetes Care* 1999;22 (Suppl 2):B35-B39.
22. Purnell JQ, Marcovina SM, Hokanson JE, et al. Levels of lipoprotein(a), apolipoprotein B, and lipoprotein cholesterol distribution in IDDM. Results from follow-up in the Diabetes Control and Complications Trial. *Diabetes* 1995;44:1218-1226.
23. Jensen-Urstad KJ, Reichard PG, Rosfors JS, Lindblad LEL, Jensen-Urstad MT. Early atherosclerosis is retarded by improved long-term blood glucose control in patients with IDDM. *Diabetes* 1996;45:1253-1258.
24. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus; a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103-117.
25. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853.
26. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-865.
27. Stratton IM, Adler AI, Neil HAW, et al, on behalf of the UK Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405-412.
28. Stratton IM, Kohner EM, Aldington SJ, et al, for the UKPDS Group. UKPDS 50: Risk factors for incidence and progression of retinopathy in type II diabetes over 5 years from diagnosis. *Diabetologia* 2001;44: 156-163.
29. Adler AI, Neil HAW, Manley SE, Holman RR, Turner RC, for the UKPDS Study Group Oxford, UK. Hyperglycemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47). *Am Heart J* 1999;138:S353-S359.
30. Standl E, Balletshofer B, Dahl B, et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia* 1996;39:1540-1545.
31. Bouma M, Dekker JH, de Sonnaville JJ, et al. How valid is fasting plasma glucose as a parameter of glycemic control in non-insulin-using patients with type 2 diabetes? *Diabetes Care* 1999;22:904-907.
32. Bonora E, Calcaterra F, Lombardi S, et al. Plasma glucose levels throughout the day and HbA_{1c} interrelationships in type 2 diabetes. *Diabetes Care* 2001;24:2023-2029.
33. Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 1997;20:1822-1826.
34. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. *Diabetes Care* 1999;22:233-240.
35. The DECODE study group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality; comparison of WHO and American Diabetic Association diagnostic criteria. *Lancet* 1999;354:617-621.
36. The DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality. Comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001;161:397-404.
37. Hanefeld M, Fischer S, Julius U, et al for the DIS Group. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 1996;39: 1577-1583.
38. Rohlfing CL, Wiedmeyer J-M, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA_{1c}. *Diabetes Care* 2002;25:275-278.
39. De Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 1995;333:1237-1241.
40. Action to Control Cardiovascular Risk in Diabetes (ACCORD). http://www.accordtrial.org

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