

Glucose control and progression of diabetic nephropathy

Date written: September 2004

Final submission: September 2005

Author: Kathy Nicholls

GUIDELINES

- a. In both Type 1 and Type 2 diabetics glycosylated haemoglobin (HbA_{1c}) should be maintained at or < 7% for primary prevention of diabetic nephropathy, and for prevention of progression from microalbuminuria to overt nephropathy. (Level I evidence for Type 1 diabetes – moderate volume; Level I evidence for Type 2 diabetes – small volume)
- b. Optimal glycaemic control - preprandial blood glucose 4.4–6.7 mmol/L and HbA_{1c} < 7% carries increased risk of hypoglycaemia. (We do not have evidence that tight control in Type 2 diabetics with overt nephropathy will alter outcome)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- The Australian Diabetes Association is attempting to standardize HbA_{1c} assays nationally. Some older assays are falsely elevated by carbamylated Hb in chronic kidney disease (CKD).
- The risk of hypoglycaemia can be minimised by frequent blood glucose monitoring with appropriate intervention (AACE).
- There is evidence that renal damage rarely occurs in patients with either Type 1 or Type 2 diabetes if HbA_{1c} is < 7.5% and postprandial blood glucose is < 10.1 mmol/L. Data from the Joslin Clinic (Type 1) suggests that a low incidence rate of diabetic nephropathy occurs when HbA_{1c} < 8.0%. Lower levels of HbA_{1c} may be required for macrovascular protection.
- A major limitation of the available data is that they do not identify the optimum level of control for particular patients, as there are individual differences in the risks of hypoglycaemia, weight gain, and other adverse effects.
- It is unclear how different components of multifactorial interventions (e.g. educational interventions, glycaemic targets, lifestyle changes, and pharmacological agents) contribute to the reduction of complications.
- There are no clinical trial data available for the effects of glycaemic control in patients with advanced complications, the elderly (> 65 years of age), or children < 13 years.
- In the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), intensive control trebled the risks of hypoglycaemia and increased weight gain.

- **Epidemiological analyses suggest that there is no lower limit of A_{1c} at which further lowering does not reduce risk of complications. However, the absolute risks and benefits of lower targets are unknown.**
- **The risks and benefits of an A_{1c} goal of < 6% are currently being tested in an ongoing study (ACCORD = Action to Control Cardiovascular Risk in Diabetes) in Type 2 diabetes.**
- **Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose (FPG) in some epidemiological studies. Postprandial plasma glucose (PPG) levels > 7.8 mmol/L are unusual in non-diabetics, although large evening meals can be followed by plasma glucose values up to 10 mmol/L.**
- **The longer patients can maintain a target HbA_{1c} level of 7.0%, which is achievable with current methods, the greater their protection from nephropathy.**

Background

Although disputed for many years, the causal relationship between poor glycaemic control and development and progression of complications is now proven, as outlined in this section.

The risk of a rapid decline of glomerular function abruptly increases when glycated haemoglobin exceeds 7.5% and postprandial blood glucose is > 11 mmol/L (Nosadini and Tonolo 2004).

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A II receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

Date of search: 16 December 2003.

What is the evidence?

Type 1 diabetes

The Diabetes Control and Complications Trial research group (DCCT 1993) conducted a 10-year prospective randomised controlled trial of intensive glucose control (target HbA_{1c} < 7%) in 1441 normotensive Type 1 diabetics with albumin excretion rate (AER) < 139 mcg/min (< 200 mg/24 hrs). Adolescents > 13 years were included. The primary (n = 726) and secondary (n = 715) cohorts were each randomised to either intensive treatment (3–4 injections of insulin or continuous subcutaneous insulin infusion and 4 self-monitored blood glucose tests daily) or conventional treatment (1–2 injections of insulin and either home urine glucose

testing several times per day, or later in the study, self blood glucose testing once per day). The DCCT was stopped prematurely in 1993, after a mean duration of follow-up of 6.5 years. Although the mean HbA_{1c} levels of the 2 DCCT treatment groups reached their maximum separation by 6 months post-randomisation, it took 3–4 years of different treatment regimens with separation of HbA_{1c} levels by 2.0%, before the cumulative incidence curves of nephropathy began to diverge distinctly.

Intensive treatment prevented the development and progression of nephropathy: the onset of proteinuria was reduced by 54% and microalbuminuria by 39%, most prominently in the primary prevention cohort. The absolute risk of nephropathy was proportional to the mean HbA_{1c} level over the follow-up period. For each 10% decrease in HbA_{1c}, there was a 25% decrease in the risk of microalbuminuria, and no glycaemic threshold for nephropathy was detected above the non-diabetic range of HbA_{1c} by any form of modeling of the data.

The DCCT found no influence of intensive treatment on GFR (¹²⁵I-iothalamate clearance) or creatinine clearance, which remained within the normal range for most subjects during the DCCT.

Further follow-up after 4 years confirmed persistent protection despite increasing hyperglycaemia. (DCCT 2000)

The DCCT patient cohort has converted to the Epidemiology of Diabetes Interventions and Complications (EDIC) observational study (DCCT 2002), which reports sustained benefits of intensive treatment well beyond the period of its most intensive implementation. Risk reduction for intensive treatment has been maintained through 7 years although HbA_{1c} levels have converged. At 1 year, the difference in mean HbA_{1c} of the 2 former randomised groups was only 0.4% (P < 0.001) - 8.3% in the former conventional treatment group vs. 7.9% in the former intensive treatment group. The difference continued to narrow, losing statistical significance by 5 years (8.1% vs. 8.2%, P = 0.09). However, the further rate of progression of complications from their levels at the end of the DCCT remains less in the former intensive treatment group on intention-to-treat analysis.

At the fifth- and sixth-year examinations of 1298 EDIC participants, the prevalence of microalbuminuria in those without it at DCCT closeout remains less in the former intensive treatment group than in the conventional treatment group (4.5% vs 12.3% , RRR 67%; P < 0.001). In subjects with either normoalbuminuria or microalbuminuria at DCCT closeout, the risk reduction in subsequent development of clinical albuminuria in the former intensive treatment group was 84% (P < 0.001). Furthermore, an aggregate endpoint of serum creatinine (0.18 mmol/L) chronic dialysis therapy, or renal transplantation, was reached by only 6 of the original intensive treatment group versus 17 of the original conventional group. While the prevalence of hypertension at the end of the DCCT was equivalent in the conventional and intensive groups (12% vs. 11%) the EDIC at 6 years documented significantly greater hypertension in the conventional group (33% vs. 25%, P < 0.001).

The Minnesota Transplant group (Barbosa et al 1994) looked at Intensive vs. standard glucose control in 48 diabetic renal transplant recipients. Good glucose control resulted in histologically-confirmed protection from subsequent nephropathy.

Type 2 diabetes

In Type 2 diabetics, only recently has good data emerged for glycaemic control protecting from microvascular complications.

In the Kumamoto Study (Ohkubo et al 1995), significantly less nephropathy developed in Type 2 diabetes patients intensively treated with insulin. This prospective 6-year study identified a primary prevention cohort (no albuminuria) and a secondary intervention cohort (overt microalbuminuria). Glycaemic control in the two groups was HbA_{1c} 7.1% vs. 9.4%; percentage of patients developing nephropathy was 8 vs. 28 in the prevention cohort, while in the microalbuminuric group, 12% vs. 28% progressed to nephropathy. However, this is one small study and the patients were thin Type 2 diabetics – we should probably not extrapolate freely from it.

The UKPDS (1998) studied 4075 newly-diagnosed Type 2 diabetic patients from 23 UK centres over 20 years. Intensive glycaemic control produced better microvascular outcome with less kidney failure, and two-thirds reduction in risk of doubling of serum creatinine. There was less development of both microalbuminuria and proteinuria in the intensive treatment group (RRR 33% for microalbuminuria development). A 37% decrease in the incidence rates of micro-macro-albuminuria was observed for any decrease of HbA_{1c} by 1% (Stratton et al 2000).

Blood Glucose Levels as well as HbA_{1c} may be important. (Level III evidence) Nosadini and Tonolo (2004) followed 74 hypertensive patients with Type 2 diabetes and elevated AERs, while achieving BP < 140/90 mmHg with ACEIs, CCBs and diuretics. Every 6 months for 4 years, GFR, HbA_{1c} and daily fasting and postprandial glucose levels were measured. GFR decreased in 75% of patients, all of whom had HbA_{1c} > 7.5%. Postprandial blood glucose was closely correlated with rapid GFR decline ($R^2 = 0.55$, $p < 0.00001$). No significant change was observed when postprandial glucose was < 10.1 mmol/L.

In Type 2 diabetes, there is no evidence that strict metabolic control retards progression once overt nephropathy is present (Parving et al 1998).

Summary of the evidence

Long-term studies, especially in Type 1, but also in Type 2 diabetic patients, indicate that good glycaemic control results in clinically significant preservation of renal function. However, benefit is greatest when control is instigated earlier in the course of nephropathy. In Type 2 diabetics with overt nephropathy, there is no evidence that tight control will alter the renal function outcome.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative (2004): No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

American Diabetes Association: HbA_{1c} < 7% (DCCT reference method). Review therapy if consistently > 8. Recommended plasma glucose ranges are 5–7.2 mmol/L pre-prandial, 6.1–8.3 mmol/L bedtime.

American Diabetes Association (Revision 2004): Aim for normoglycaemia, HbA_{1c} < 7% (B), and consider < 6% in individual patients (B), but less stringent goals may be appropriate for patients with severe hypoglycaemia, limited life expectancies, or comorbid conditions, and for very young children or older adults (E).

American Association of Clinical Endocrinology: HbA_{1c} < 7%.

Canadian Diabetes Association: “Best possible glucose control” recommended in all diabetics for prevention, onset and delay in progression of early nephropathy. (Grade A, level 1A) Therapy in most patients with Type 1 or 2 diabetes should be targeted to achieve HbA_{1c} ≤ 7.0% in order to reduce the risk of microvascular (Grade A, Level 1A0 and macrovascular complications (Grade C, level 3).

To achieve A_{1c} ≤ 7.0%, aim for FPG or preprandial PG targets of 4–7 mmol/L, and 2-hr post prandial PG targets of 5–10 (Grade B, Level 2).

If it can safely be achieved, lowering PG targets toward the normal range should be considered (Grade C, Level 3): A_{1c} ≤ 6.0 (grade D, consensus), FPG/preprandial PG 4–6 (grade D, consensus) 2-hr postprandial PG 5–8 (grade D, consensus).

Australian Paediatric Endocrinology Group (2005): HbA_{1c} target < 7.5% for older children & adolescents, younger children “may set a little higher”. Blood Glucose > 4.0 mmol/L

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

American Diabetes Association: Standards of medical care in diabetes - Diabetes Care 2004; 27(Suppl 1): S15–S35.

Australasian Paediatric Endocrine Group. Clinical practice guidelines: Type 1 diabetes in children and adolescents. 2005. Available from <http://www.chw.edu.au/prof/services/endocrinology/apeg/>.

Barbosa J, Steffes MW, Sutherland DE et al. Effect of glycemic control on early diabetic renal lesions. A 5-year randomized controlled clinical trial of insulin-dependent diabetic kidney transplant recipients. JAMA 1994; 272: 600–6.

Canadian Diabetes Association. 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Available from <http://www.diabetes.ca/cpg2003/default.aspx>.

Nosadini R, Tonolo G. Relationship between blood glucose control, pathogenesis and progression of diabetic nephropathy. J. Am. Soc. Nephrol 2004; 15 (Suppl 1): S1–S5.

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 randomised prospective 6-year study. Diabetes Res Clin Pract 1995; 28: 103–17.

Parving HH. Renoprotection in diabetes: genetic and non-genetic risk factors and treatment. Diabetologia 1998; 41: 745–59.

Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405–412.

The Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342: 381–89.

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. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977–86.

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: 854–65.

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 837–53.

Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group:
Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002; 287: 2563–69.

OUT-OF-DATE

Appendix

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Barbosa et al, 1994	99	Randomised controlled clinical trial	University hospital, US	48 Type 1 diabetics with terminal diabetic renal failure undergoing renal transplantation	Subcutaneous insulin given several times a day or continuously	Subcutaneous insulin once or twice per day	5 yrs	
DCCT, 1993	1441	Randomised controlled clinical trial	29 centres	1441 insulin-dependent diabetes mellitus patients	Intensive therapy ≥ 3 insulin injections daily plus frequent blood glucose monitoring	Conventional therapy, 1-2 insulin injections daily	6.5 yrs	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Barbosa et al, 1994	Not specified	No	No	Unclear	No	52
DCCT, 1993	Not specified	Yes	Yes	Yes	No	1

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Barbosa et al, 1994	SBP (mmHg) at 5 yrs	131 (7)	129 (9)	2.00 (95%CI: -2.59, 6.59)
	DBP (mmHg) at 5 yrs	77 (6)	75 (8)	2.00 (95%CI: -2.03, 6.03)
	Glomerular morphometric measure at 5 yrs (GBM width [nm])	430 (73)	475 (181)	-45.00 (95%CI: -124.31, 34.31)
	Glomerular structural change (GBM width [nm])	91 (73)	148 (166)	-57.00 (95%CI: -130.63, 16.63)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Barbosa et al, 1994	Mortality	7/52	8/47	0.79 (95%CI: 0.31, 2.01)	-0.04 (95%CI: -0.18, 0.11)
	Graft loss / chronic rejection	2/52	2/47	0.90 (95%CI: 0.13, 6.16)	0.00 (95%CI: -0.08, 0.07)
DCCT, 1993	Proliferative or severe non-proliferative retinopathy in primary prevention cohort	2/348	4/378	0.54 (95%CI: 0.10, 2.95)	0.00 (95%CI: -0.02, 0.01)
	Clinically important macular oedema	1/348	4/378	0.27 (95%CI: 0.03, 2.42)	-0.01 (95%CI: -0.02, 0.00)