Glucose control and progression of diabetic nephropathy

Date written: September 2004
Final submission: September 2005
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GUIDELINES

a. In both Type 1 and Type 2 diabetics glycosylated haemoglobin (HbA\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{1c} < 8.0%. Lower levels of HbA\textsubscript{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.
Epidemiological analyses suggest that there is no lower limit of A1C 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 A1C 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 HbA1c 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 HbA1c < 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 HbA1c 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 HbA1c.
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 HbA1c level over the follow-up period. For each 10% decrease in HbA1c, there was a 25% decrease in the risk of microalbuminuria, and no glycaemic threshold for nephropathy was detected above the non-diabetic range of HbA1c 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 HbA1c levels have converged. At 1 year, the difference in mean HbA1c 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 HbA1c 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 HbA1c by 1% (Stratton et al 2000).

Blood Glucose Levels as well as HbA1c 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, HbA1c and daily fasting and postprandial glucose levels were measured. GFR decreased in 75% of patients, all of whom had HbA1c > 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?


UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

American Diabetes Association: HbA1c<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


Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group:
### Appendix

**Table 1** Characteristics of included studies

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

**Table 2** Quality of randomised trials

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Method of allocation concealment</th>
<th>Blinding (participants)</th>
<th>Blinding (investigators)</th>
<th>Blinding (outcome assessors)</th>
<th>Intention-to-treat analysis</th>
<th>Loss to follow up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbosa et al, 1994</td>
<td>Not specified</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>52</td>
</tr>
<tr>
<td>DCCT, 1993</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</table>
### Table 3 Results for continuous outcomes

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

### Table 4 Results for dichotomous outcomes

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