A Systematic Review of Recent Data Describing the Risk of Complications in Type 1 Diabetes Mellitus Patients

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ABSTRACT

Objective: To identify recent data describing the long-term risk of complications in patients with type 1 diabetes mellitus (T1DM) and their association with glycosylated haemoglobin (HbA_{1c}) and other risk factors, and to select complications and related data for inclusion in a new cost-utility model for T1DM.

Methods: A systematic review was performed. The following electronic databases were searched (1 January 2003-27 July 2011): MEDLINE, MEDLINE In-Process, EMBASE, and the Cochrane Library, including the Health Technology Assessment (HTA) database. Relevant clinical guidelines and HTA documentation also were searched.

Results: A total of 4,846 titles were screened; 281 reports of 72 unique studies were included for qualitative synthesis. Multiple reports were identified for several studies, including the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) follow-up study, the Epidemiology of Diabetes Complications (EDC) study, the Finnish Diabetic Nephropathy (FinnDiane) study, the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the Epidemiology and Prevention of Diabetes in Europe (EURODIAB) type 1 complications study, and several other large observational and registry studies. Data were extracted for 57 T1DM complications in adults and 20 in children and adolescents. Complications were selected for inclusion in the cost-utility model where there was evidence for a statistical association between T1DM and HbA_{1c} levels and an expected impact on mortality, costs, and/or health-related quality of life. The following complications were selected: cardiovascular disease, peripheral neuropathy, renal disease, retinopathy, cataract, hypoglycaemia, ketoacidosis, and adverse birth outcomes.

Conclusions: Since 2003, 281 reports of 72 studies (including many large, observational studies) have been published. These reports have substantially increased the available evidence describing complications in patients with T1DM. The DCCT/EDIC studies uniquely provide long-term follow-up (now more than 23 years) of patients managed using strategies that best represent contemporary T1DM management.

OBJECTIVES

- To identify recent data describing the long-term risk of complications in patients with type 1 diabetes mellitus (T1DM) and their association with glycosylated haemoglobin (HbA_{1c}) and other risk factors.
- To select complications and related data for inclusion in a new cost-utility model for T1DM.

METHODS

- A systematic review was performed to a prespecified protocol.
- Searches were performed of MEDLINE, MEDLINE In-Process, EMBASE, and the Cochrane Library, including the Health Technology Assessment (HTA) database. Relevant clinical guidelines were reviewed for pertinent data.[1-4] Database searches were performed from 1 January 2003 to 27 July 2011, because NICE Clinical Guideline 15 reviewed evidence published up to 27 May 2003.[4]
- Search terms included combinations of free-text and Medical Subject Headings (MeSH) terms for T1DM (including "Diabetes Mellitus, Type 1" [MeSH], type I diabet*[Title/Abstract], and "IDDM"[Title/Abstract]) and natural history (including "Natural History"[MeSH] and "natural history"[Title/Abstract]).
- Study inclusion and exclusion criteria are presented in Table 1. No restrictions were made in terms of T1DM treatment.

Table 1. Inclusion and Exclusion Criteria

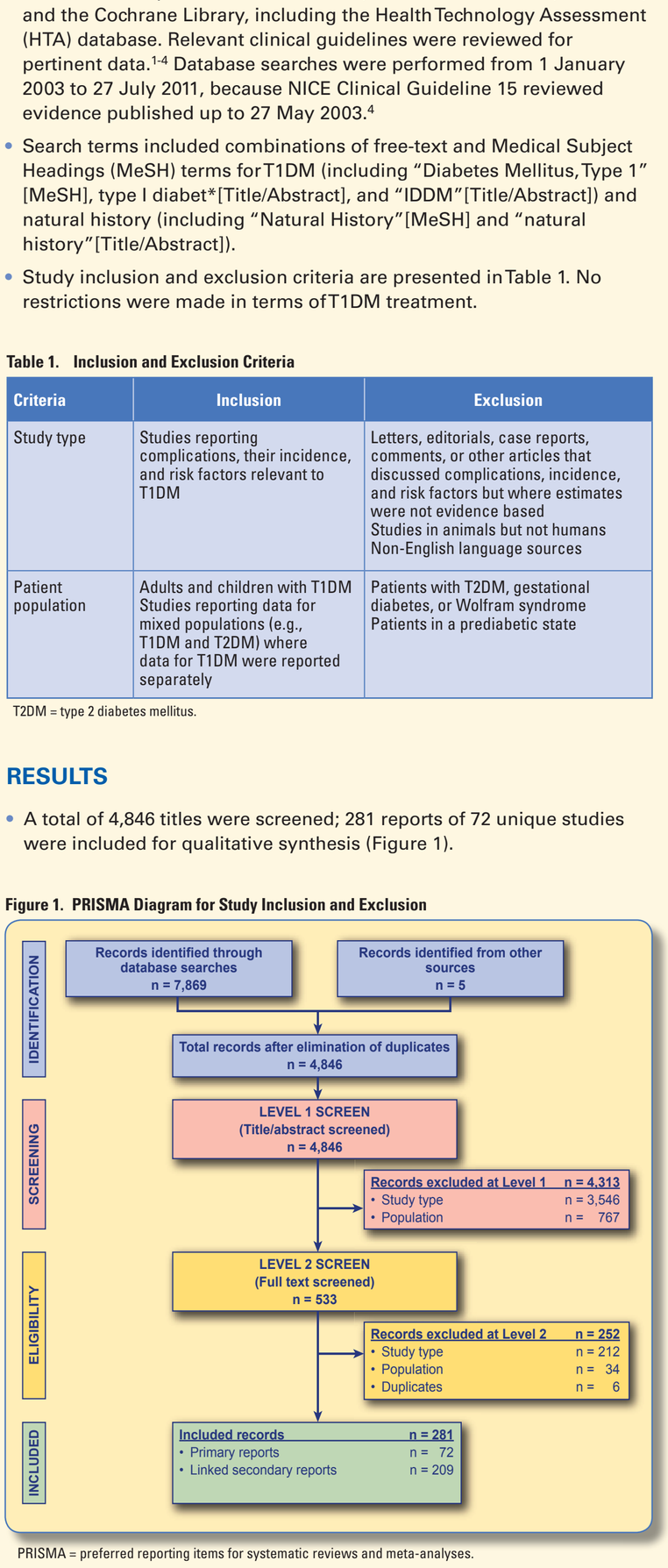
Criteria	Inclusion	Exclusion
Study type	Studies reporting complications, their incidence, and risk factors relevant to T1DM	Letters, editorials, case reports, comments, or other articles that discussed complications, incidence, and risk factors but where estimates were not evidence based Studies in animals but not humans Non-English language sources
Patient population	Adults and children with T1DM Studies reporting data for mixed populations (e.g., T1DM and T2DM) where data for T1DM were reported separately	Patients with T2DM, gestational diabetes, or Wolfram syndrome Patients in a prediabetic state

T2DM = type 2 diabetes mellitus.

RESULTS

- A total of 4,846 titles were screened; 281 reports of 72 unique studies were included for qualitative synthesis (Figure 1).

Figure 1. PRISMA Diagram for Study Inclusion and Exclusion



PRISMA = preferred reporting items for systematic reviews and meta-analyses.

- Multiple reports were identified for several large studies with long-term follow-up. Studies for which the most data and analyses have been reported are summarised in Table 2.
- Data were extracted for 57 T1DM complications in adults and 20 in children and adolescents, and the individual complications were grouped together (Table 3).
- Complications were selected for inclusion in the cost-utility model where there was evidence for a statistical association with T1DM, an association with HbA_{1c}, and an impact on mortality, costs and/or health-related quality of life (HRQOL).
- The following complications were selected for inclusion in the model: cardiovascular disease (a composite endpoint of nonfatal MI, stroke, death from cardiovascular disease, confirmed angina, or the need for coronary artery revascularisation); cataract; hypoglycaemia; ketoacidosis; peripheral neuropathy; pregnancy, birth outcomes; renal disease; and retinopathy.
- Additional risk factors for T1DM complications other than HbA_{1c} included age, age at onset of T1DM, duration of diabetes, body mass index, and sex.

Table 2. Key Identified Studies

Study	Number of Publications	Methods	Outcomes
DCCT and EDIC	53	• 1,441 patients with T1DM enrolled between 1983 and 1989 • Patients followed up in the EDIC study • Follow-up now more than 23 years • Interventions were intensive therapy (3 or more insulin injections daily or the use of an insulin pump) or conventional therapy (1 or 2 daily injections of insulin)	• Main study outcome was the first cardiovascular event, defined as nonfatal myocardial infarction (MI), stroke, angina, coronary revascularisation procedures, or death due to cardiovascular disease
EDC	19	• 18-year prospective study of a cohort with childhood-onset diabetes • 658 participants diagnosed between 1950 and 1980	• Complications evaluated included nephropathy, cardiovascular and peripheral vascular disease, clinical neuropathy, and proliferative retinopathy
FinnDiane	16	• Finnish national cross-sectional and prospective study of 8,000 patients with T1DM started in 1998 • Recruitment status at approximately 4,600 patients; study expected to end in 2020	• Evaluated clinical, environmental, and genetic risk factors for T1DM and its microvascular and macrovascular complications
Wisconsin Epidemiologic Study of Diabetic Retinopathy	14	• Population-based survey of 10,135 patients with T1DM and T2DM in southern Wisconsin in 1979-1980 • Many reports for this study provided data for patients with T1DM separately	• Evaluated the prevalence, incidence, and progression of diabetic retinopathy and its component lesions, and determined the relationships between incidence and progression of diabetic retinopathy and risk factors
EURODIAB	9	• 3,250 patients with T1DM from 16 European countries • Baseline examinations performed between 1989 and 1991 • The EURODIAB Prospective Diabetic Peripheral Neuropathy Study followed prospectively for 7.3 years 1,172 patients with no peripheral neuropathy at baseline	• Evaluated the incidence of diabetic neuropathy and the risk factors associated with an increased risk of diabetic neuropathy
Other large observational studies	56	NA	NA
Other studies	114	NA	NA

DCCT = Diabetes Control and Complications Trial; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications study; EURODIAB = Epidemiology and Prevention of Diabetes in Europe; FinnDiane = Finnish Diabetic Nephropathy; NA = not applicable.

Table 3. Complications Reported by Included Studies

Complication	Associated With T1DM	Prevented by Glycemic Control and/or Independent Association With HbA_{1c}	Selected for Inclusion in the Economic Model	Reason for Exclusion
Anxiety and depression	Unclear: conflicting evidence, possibly confounded by comorbidities	Unclear: association demonstrated but causality is questionable	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Autoimmune thyroiditis	Yes: ~10% of patients require treatment; screening programmes in place in some countries[5,6]	Unclear: not investigated	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM; minor impact on costs and HRQOL
Cardiovascular disease	Yes: angina, hypertension, MI, and stroke[7]	Yes: the decrease in HbA_{1c} values during DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease[8]	Yes	NA
Carpal tunnel syndrome	Yes: predicted lifetime risk was ~85% after 54 years of T1DM[9]	No: there was no demonstrable effect of glycaemic control on incidence of carpal tunnel syndrome[9]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM; relatively minor impact on HRQOL
Cataract	Yes: 25-year crude cumulative incidence of cataract surgery was ~20%[10]	Yes: the hazard ratio for risk of cataract surgery was 1.22 (95% CI 0.91-1.64) [reported value inverted to give to give the HR for a 1% increase in HbA_{1c}][10]	Yes	NA
Cognitive dysfunction	Unclear: conflicting evidence	Unclear: association demonstrated but cause and effect not established	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Cutaneous manifestations	Yes: there was higher prevalence in patients with T1DM than in control subjects[11]	No: there was no evidence to relate diabetic hand to metabolic control[11]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Female sexual dysfunction	Unclear: conflicting evidence	Unclear: conflicting evidence	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Male sexual dysfunction	Unclear: limited evidence, only 1 study identified[12]	Unclear: limited evidence, only 1 study identified[12]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Fracture	Unclear: conflicting evidence	Unclear: no evaluation of the impact of HbA_{1c} levels on fracture risk identified	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Hypoglycaemia	Yes: reported severe hypoglycaemia (coma or seizure) rates ranged from 5.4% to 19.0% per 100 patient-years in the EDIC, DCCT, and EDC T1DM populations[13]	Yes: HbA_{1c} was inversely related with rate of severe hypoglycaemia with an effect corresponding to an RR of 1.4 in the lowest HbA_{1c} quartile compared with the upper quartile[14]	Yes	NA
Ketoacidosis	Yes: rate of ketoacidosis events reported in DCCT, EDIC, and EDC ranged from 0% to 3.1% per 100 patient-years[13]	Yes: HbA_{1c} was a significant predictor of ketoacidosis ($P = 0.001$)[15]	Yes	NA
Limited joint mobility	Unclear: limited evidence, only 1 study identified[16]	Unclear: limited evidence, only 1 study identified[16]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Myopia	Unclear: limited evidence, only 1 study identified[17]	Unclear: limited evidence, only 1 study identified[17]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Nonalcoholic fatty liver disease	Unclear: limited evidence, only 1 study identified[18]	Unclear: limited evidence, only 1 study identified[18]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Peripheral neuropathy, foot ulcer, and amputation	Yes: incidence rate for lower extremity amputation was 3.2% (95% CI, 1.2-9.4) per 1,000 patients with T1DM[19]	Yes: higher HbA_{1c} (per 1% OR, 1.40; 95% CI, 1.24-1.58) was independently associated with the incidence of lower extremity amputation[20]	Yes	NA
Pregnancy, birth outcomes	Yes: the congenital malformation rate was 5.0% in the T1DM population and 2.8% (RR, 1.7; 95% CI, 1.3- 2.2) in the background population[21]	Yes: for HbA_{1c} levels > 7%, there was an almost linear association between HbA_{1c} and risk of adverse pregnancy outcome, whereby a 1% increase in HbA_{1c} corresponded to 5.5% (95% CI, 3.8–7.3) increased risk of adverse pregnancy outcome[22]	Yes	NA
Renal disease	Yes: there was a 5-year incidence of renal replacement therapy of 10.2% in patients with T1DM recruited to the ETDRS trial[23]	Yes: a 1% increment in HbA_{1c} level was a significant risk factor of renal replacement therapy ($P \leq 0.01$)[23]; the adjusted HR for microalbuminuria per 1% increase in HbA_{1c} was 1.80 (95% CI 1.54-2.10)[24]	Yes	NA
Retinopathy	Yes: there was a cumulative incidence of 84.1% for any retinopathy and 50.2% for advanced retinopathy after 40 years of T1DM[25]	Yes: an HbA_{1c} level of > 7.5% was a significant risk factor for both any retinopathy and advanced retinopathy ($P < 0.0001$)[25]; progression of diabetic retinopathy also was more likely after an increase in the HbA_{1c} level[26]	Yes	NA
Sleep disturbances	Unclear: limited evidence, only 1 study identified[27]	Unclear: limited evidence, only 1 study identified[27]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Urinary incontinence	Unclear: limited evidence, only 1 study identified[28]	Unclear: limited evidence, only 1 study identified[28]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM
Urinary tract infections/ symptoms	No: sexual activity, rather than measures of diabetes control and complications, was the main risk factor for urinary tract infection[29]	No: no association was observed between HbA_{1c} levels at the DCCT baseline or end of study or at the year 10 EDIC examination (urological assessment component of the EDIC)[30]	No	Insufficient evidence that effective diabetes management reduces the risk of T1DM

CI = confidence interval; ETDRS = Early Treatment of Diabetic Retinopathy Study; HR = hazard ratio; NA = not applicable; OR = odds ratio; RR = relative risk.

CONCLUSIONS

- Since 2003, 281 reports of 72 studies (including many large, observational studies) have been published. These reports have substantially increased the available evidence describing complications in patients with T1DM.
- The DCCT/EDIC studies uniquely provide long-term follow-up (now more than 23 years) of patients managed using strategies that best represent contemporary T1DM management.

REFERENCES

Please see handout for a complete reference list.

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