Interventions for Diabetic Retinopathy in Type 1 Diabetes: Systematic Review and Meta-Analysis

SOHAIB A. VIRK, KIM C. DONAGHUE, TIEN Y. WONG, AND MARIA E. CRAIG

• PURPOSE: To systematically review the effectiveness of systemic interventions for diabetic retinopathy (DR) in type 1 diabetes.
• DESIGN: Systematic review and meta-analysis.
• METHODS: MEDLINE, EMBASE and Cochrane Library were searched for studies published from January 1990 to December 2014. Randomized controlled trials and controlled cohort studies reporting incidence or progression of DR following systemic intervention were included. Two reviewers selected studies, extracted data, and assessed risk of bias. For each intervention, pooled outcomes were reported as relative risk (RR) estimates with 95% confidence intervals (CI).
• RESULTS: Twenty-four studies involving 9302 patients met inclusion criteria. Incident DR was reduced by intensive vs conventional insulin therapy (RR 0.43; 95% CI 0.23–0.83), insulin pumps vs multiple daily injections (RR 0.45; 95% CI 0.24–0.83), and angiotensin receptor blockade vs placebo (RR 0.65; 95% CI 0.49–0.85). The benefit of insulin pumps over multiple daily infections was independent of HbA1c. DR progression was reduced by intensive vs conventional insulin therapy (RR 0.63; 95% CI 0.43–0.92), angiotensin-converting enzyme inhibition vs placebo (RR 0.60; 95% CI 0.41–0.86), and islet cell transplantation vs medical therapy (RR 0.25; 95% CI 0.08–0.71).
• CONCLUSIONS: Intensive insulin therapy, and specifically insulin pump therapy vs multiple daily injections, prevents DR in both adults and adolescents with type 1 diabetes. Antihypertensive agents provide protection in normotensive, normoalbuminuric adults. In patients with type 1 diabetes of longer duration, islet cell transplantation may be more effective than medical therapy. There is insufficient evidence for antilipid therapy or other systemic interventions. (Am J Ophthalmol 2015;160(5):1055–1064. © 2015 by Elsevier Inc. All rights reserved.)

DIABETIC RETINOPATHY (DR) IS THE MOST SERIOUS ocular complication of type 1 diabetes and the leading cause of acquired blindness in working-age adults.[1] It progresses through distinct stages, from early nonproliferative retinal changes to proliferative disease marked by neovascularization of the retina. Early retinopathy is present in around 12%–15% of adolescents with type 1 diabetes.[2,3] By 20 years duration, the majority of adults with type 1 diabetes display some form of DR,[1,4] with one-third to one-half of these developing vision-threatening disease.[4]

Duration of diabetes is one of the strongest predictors for the development and progression of DR, while hyperglycemia, hypertension, and dyslipidemia are well-established modifiable risk factors.[5] Persistently elevated levels of glycosylated hemoglobin (HbA1c), blood pressure, and serum triglycerides contribute to the cascade of pathophysiological processes that induce the microvascular damage and retinal dysfunction characteristic of DR.[1]

The prevention of DR in type 1 diabetes is currently heavily dependent on tight glycemic control, while the role of antihypertensive agents, antilipid therapy, and other systemic interventions remains unclear. Previous reviews of interventional studies have either predated major clinical trials[5,6] or focused exclusively on intensive glycemic control as the major outcome measure.[6,7] This is problematic, as tight glycemic control alone—while effective—is difficult to achieve in practice, with fewer than half of type 1 diabetes patients able to maintain an HbA1c level <7.5% (58 mmol/mol).[7] To date, there have been no meta-analyses examining the role of other systemic interventions for DR.

Thus our objectives were to systematically review the evidence for the effectiveness of systemic interventions in preventing either the incidence or progression of DR in people with type 1 diabetes.

METHODS

• DATA SOURCES AND SEARCHES: Electronic databases, including MEDLINE, EMBASE, and Cochrane Central

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Jul 15, 2015.

From the Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia (S.A.V., K.C.D., M.E.C.); School of Women's and Children's Health, University of New South Wales, Sydney, Australia (S.A.V., M.E.C.); Discipline of Pediatrics and Child Health, University of Sydney, Sydney, Australia (K.C.D., M.E.C.); and Singapore Eye Research Institute, Singapore National Eye Center, Duke-NUS Graduate Medical School, National University of Singapore, Singapore (T.Y.W.).

Inquiries to Professor Maria E. Craig, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Locked Bag 4001, Westmead 2145, New South Wales, Australia; e-mail: m.craig@unsw.edu.au

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2015.07.024

Register of Controlled Trials, were searched from January 1, 1990 to December 31, 2014 (Ovid Technologies, Inc, New York City, NY). The search terms "type 1 diabetes OR IDDM OR T1D OR T1DM" were combined with "diabetic retinopathy OR ((diabetes or diabetic or DM) AND (retinopathy))" as both keyword and MeSH (Medical Subject Headings) terms. This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies.

Two investigators (S.V. and M.C.) independently screened the title and abstract of records identified in the search. Full-text publications were sought and reviewed for studies identified by either reviewer as being potentially eligible. Disagreements about final study inclusion were resolved by consensus.

• **STUDY SELECTION:** Eligible studies were those in which study participants (of any age) with type 1 diabetes underwent ophthalmologic assessment prior to receiving an intervention aimed at modifying either the incidence or progression of DR, either as a primary or secondary outcome.

Only published comparative reports with concurrent controls, not receiving the intervention of interest, were considered. This encompassed nonrandomized and randomized controlled trials (RCTs), as well as controlled cohort studies. Studies were included if they reported the number of patients in both experimental and control groups who experienced either development or progression of DR. Studies were included in the incidence analysis if patients were free of DR at baseline, while patients with preexisting DR were allocated to the progression analysis. A minimum follow-up duration of 1 year was imposed to ascertain longer-term outcome. When authors published duplicate studies with longer follow-up duration, only the most complete reports were included.

Exclusion criteria were (1) focal ophthalmologic treatments such as laser photocoagulation and surgical vitrectomy, since our review focused on systemic preventative interventions; (2) studies that only reported data on other ophthalmologic measures (such as visual acuity, macular thickness, or blood-retina barrier permeability); (3) interventions administered exclusively during pregnancy, given that pregnancy itself is a risk factor for DR[8]; (4) non-English papers, unless the English abstract provided enough information to establish eligibility; (5) studies with fewer than 5 patients in either comparison arm; and (6) studies examining mixed populations or multiple retinal conditions, if separate data for DR in type 1 diabetes could not be obtained after contacting the corresponding authors.

• **DATA EXTRACTION AND QUALITY ASSESSMENT:** Data extracted from each trial included information on: study design, participants (age, sex, duration of diabetes, and baseline HbA1c), description and duration of intervention, nature of control group, method of DR assessment, incidence or progression of DR in each group, and adverse events reported. If these data could not be obtained from either the full text or figures/tables in the article, the corresponding authors were contacted.

The risk of bias in included studies was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations adapted for randomized and nonrandomized interventional studies.[9] Study quality assessment addressed selection bias, masking, attrition rate, and accuracy of outcome assessment.

• **OUTCOME MEASUREMENT:** We defined incidence and progression of DR as at least 3-level worsening from baseline on the modified Airlie House classification scale used in the Early Treatment Diabetic Retinopathy Study.[10] This classification system is the gold standard for assessment of DR in clinical trials[11] and is based on grading of 7-field stereoscopic images of the retina, with each image compared to standardized photographs. A level of DR severity is then assigned to each eye, ranging from 10 (no DR) to 85 (advanced proliferative DR). The number of levels used within the scale varies from study to study, depending on the specific modifications made to the Airlie House classification system. The 3-level endpoint was chosen because it represents clinically significant disease progression[12] and has been adopted by almost all major trials investigating DR, enabling comparisons across the included studies for quantitative synthesis. For studies using different adaptations of the Airlie House classification system, the level of worsening that was most equivalent was reported in our analysis. As our review focused on systemic interventions, outcomes were reported using the person (not eye) as the unit of analysis.

• **DATA SYNTHESIS AND ANALYSIS:** The relative risk (RR) was used as a summary statistic, with 95% confidence intervals (CI). The meta-analyses were performed using random-effects models to take into account anticipated clinical and methodological diversity between studies. The I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance, with values exceeding 50% indicative of considerable heterogeneity.[13] When the same interventions were used in both cohort studies and RCTs, subgroup analysis was performed by study design. Although further subgroup and sensitivity analyses were planned to account for other potential confounders, this was not possible owing to the limited number of studies and lack of raw data. All *P* values were 2-sided. Statistical analyses were conducted with Review Manager Version 5.2.1 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

RESULTS

WE IDENTIFIED 7841 RECORDS THROUGH ELECTRONIC searches and 6 through manual searches, 6911 of which remained after the removal of duplicates (Supplemental Figure 1, available at AJO.com). Of these, 6810 records