Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus

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CRD summary

The review concluded that, in adults with type 2 diabetes, intensive glucose control reduced the risk for microalbuminuria and macroalbuminuria, but evidence was lacking for a reduction in risk for significant clinical renal outcomes. Despite the possibility of missing studies affecting the accuracy of the review results, the authors' conclusions nevertheless appear likely to be reliable.

Authors' objectives

To evaluate the benefits of intensive versus conventional glucose control on kidney-related outcomes for adults with type 2 diabetes.

Searching

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from 1950 to December 2010; search terms were reported. The reference lists of identified articles, previous meta-analyses and original studies identified by the search were also checked to find other potentially eligible studies. Review articles and the Web of Science database were searched to find all relevant follow-up articles.

Study selection

Randomised controlled trials (RCTs) of intensive lowering of glucose versus a standard regimen (placebo, standard care, or glycaemic control of reduced intensity) in adults (19 years or older) with stable type 2 diabetes in an out-patient setting were eligible. Studies had to assess progression or development of kidney disease and report sufficient outcome data to allow extraction or calculation of effect estimates for its progression or new diagnosis.

Mean baseline serum creatinine levels ranged from 0.9 to 1.0mg/dL. Mean duration of disease before enrolment ranged from 6.5 to 12 years (except for one trial which recruited newly diagnosed patients). The interventions to achieve intensive glycaemic control varied and included insulin, metformin, sulphonylurea, gliclazide or various drug combinations. Duration of treatment ranged from two to 11.1 years. Most studies were conducted in the UK or North America.

Two reviewers independently selected studies for inclusion.

Assessment of study quality

A risk of bias assessment was performed based on the components of the Cochrane risk of bias tool: allocation concealment; blinding; completeness of outcome data reporting; selective reporting of outcomes; and other sources of bias.

It appeared that one reviewer performed the assessment, which was then checked by a second reviewer.

Data extraction

Data were extracted to calculate risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CI). Authors were contacted to clarify details when necessary.

One reviewer extracted data which were then checked by a second reviewer.

Methods of synthesis

Meta-analyses were performed to calculate pooled risk ratios, or risk differences (with 95% confidence intervals) using a random-effects model. Heterogeneity was assessed using I^2. Meta-regressions were performed to examine the effect on outcomes of: median date of enrolment, years since diagnosis, duration of therapy, difference in achieved HbA1c and median achieved HbA1c. Sensitivity analyses explored the impact of risk of bias assessment results, and of

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excluding each study in turn. Publication bias was assessed using funnel plots.

Results of the review

Seven RCTs were included (28,065 participants; range 110 to 11,140). Median follow up periods ranged from two to 11.1 years. Most studies had a low risk of bias rating for all domains of the Cochrane risk of bias tool, except for blinding of participants and personnel, where all but two studies were subject to a high risk of bias.

Compared with conventional treatment, intensive glucose control statistically significantly reduced the risk of microalbuminuria (RR 0.86, 95% CI 0.76 to 0.96, seven trials, I^2=64%) and macroalbuminuria (RR 0.74, 95% CI 0.65 to 0.85, six trials, I^2=13%), but there were no significant differences for the clinical renal outcomes: doubling of the serum creatinine level (four trials), end-stage renal disease (five trials) and death from renal disease (three trials). The result for macroalbuminuria was not significant when only the two studies with adequate participant/personnel blinding were used in the analysis. Other risk of bias sensitivity analyses had little effect on the results.

Meta-regression indicated that larger differences in haemoglobin A1c between intensive and conventional therapy were associated with greater benefit for both microalbuminuria and macroalbuminuria. The median year of enrolment, the years since diabetes diagnosis and the duration of therapy were only associated with the doubling of the serum creatinine level outcome.

Funnels plots suggested there was evidence of publication bias.

Authors' conclusions

Intensive glucose control reduced the risk for microalbuminuria and macroalbuminuria, but evidence was lacking that it reduced the risk of significant clinical renal outcomes, such as doubling of the serum creatinine level, end-stage renal disease or death from renal disease during the years of follow-up of the trials.

CRD commentary

The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken by searching electronic databases and other means. It was unclear whether unpublished studies or grey literature were specifically sought and there was an indication that publication bias may have affected the pooled estimates. Suitable methods were employed to reduce the risks of reviewer error and bias throughout the review.

Study quality was assessed and was used in interpreting the results of the review. Appropriate methods were used to pool data and to assess and investigate heterogeneity. Sufficient study details were provided with respect to most characteristics, but it was unclear which types of conventional treatment were used in individual studies, which made it more difficult to interpret the pooled results (although the haemoglobin A1c levels for each treatment group were provided). Although the possibility of missing studies and publication bias affecting the results should be acknowledged, no beneficial effects were found for the clinically meaningful and most important outcomes. The authors' conclusions appeared likely to have been reliable.

Implications of the review for practice and research

Practice: The authors stated that there was little compelling reason to initiate intensive glycaemic control in mid stage of the disease with the aim of preventing renal failure.

Research: The authors did not state any implications for research.

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