Treating prediabetes with metformin: systematic review and meta-analysis

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CRD summary
The authors concluded that metformin reduced the rate of conversion from prediabetes to type 2 diabetes mellitus. The findings were consistent and robust to rigorous sensitivity analyses. However, given the small number of trials in the review and the rather limited search, these conclusions should be interpreted with a degree of caution.

Authors' objectives
To determine the effectiveness of metformin in preventing or delaying the onset of type 2 diabetes among people with prediabetes.

Searching
MEDLINE was searched from 1966. Search terms were reported. The reference lists of relevant articles and reviews were checked. The search was not limited by language.

Study selection
Randomised controlled trials (RCTs) of metformin for delaying or preventing type 2 diabetes were eligible for inclusion, provided participants had impaired glucose tolerance or impaired fasting glucose. Trials were required to report development of diabetes as an outcome and to have a follow-up of at least six months.

Participants in the review were men and women aged between 25 and 60 years, with either impaired glucose tolerance or raised fasting plasma and postprandial glucose. They comprised subgroups or selected arms from larger trials. The trials were conducted in China, India and among a predominantly white or African American population. The intervention in the included trials was metformin 250 or 850mgs twice or three times daily, with or without lifestyle education. Controls received placebo plus lifestyle education, or standard health care advice only. Duration of follow-up was three years for most participants, although one trial had only twelve-month follow-up.

The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
It appeared that the following aspects of trial validity were considered: blinding, follow-up rate, and use of intention-to-treat analysis.

The assessment was conducted independently by two reviewers.

Data extraction
Odds ratios (ORs) were calculated from the numbers of events in the control and intervention groups of each trial, with 95% confidence intervals (CIs). Relative and absolute risk reductions and numbers needed to treat (NNT) were also calculated. Initial analyses were based on the numerators and denominators reported by the primary trials (non intention-to-treat data), but data were also analysed for each study using an intention-to-treat approach which assumed a worst-case scenario for losses to follow-up.

Data were extracted independently by two reviewers.

Methods of synthesis
Trials were combined to calculate pooled odds ratios and 95% confidence intervals based on non intention-to-treat data. A sensitivity analysis was also conducted, using an intention-to-treat analysis/worst-case scenario approach. Subgroup analyses were conducted among placebo-controlled trials and those using a low dose of metformin.
Results of the review

Three RCTs were included in the review (n=2,510 participants, range 90 to 2,155). Only one trial used intention-to-treat analysis. Two trials were blinded (i.e. placebo-controlled) and one was not. Follow-up rates ranged from 73.3 to 99.6%.

**Metformin versus placebo/usual care** (three RCTs): The risk of developing type 2 diabetes was significantly lower in the intervention group (OR 0.65, 95% CI 0.55 to 0.78; NNT 12, 95% CI 9 to 21). Results were similar using intention-to-treat analysis with a worst-case scenario (OR 0.69, 95% CI 0.58 to 0.82; NNT 12, 95% CI 9 to 22).

The statistical significance of the findings did not change when analysis was restricted to trials using a low dose of metformin or to placebo-controlled studies.

There was no significant statistical heterogeneity in any of the analyses.

**Authors’ conclusions**

Metformin reduced the rate of conversion of prediabetes to type 2 diabetes mellitus.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies without language restriction. However, the search was limited to one database and no specific attempts were made to retrieve unpublished studies, so it was possible that some studies were missed. No end date for the search was stated. Also, no formal test for publication bias was reported. Steps were taken to minimise reviewer bias and error by having more than one reviewer independently assess trial validity and extract data, but it was not clear whether these precautions also applied to the process of study selection. Criteria for validity assessment were not described in detail and some important aspects of validity (such as sequence generation and allocation concealment) were not reported.

Suitable statistical techniques were used to combine the trials, explore the effect of imputing missing data and investigate clinical and methodological differences between the trials; it was apparent from examination of the forest plots that heterogeneity was low in the main analyses. Issues concerning the applicability and implications of the review findings were well addressed in the discussion section. The findings were consistent and robust to rigorous sensitivity analyses. However, given the small number of trials in the review and the rather limited search, the authors’ conclusions should be interrupted with a degree of caution.

**Implications of the review for practice and research**

**Practice**: The authors stated that metformin could be used on a population basis to reduce rates of conversion from prediabetes to diabetes. They recommend a dose of 850mgs twice daily, except in south Asians for whom a lower dose may be more appropriate.

**Research**: The authors stated that a well-powered study should determine whether the reduction in progression to diabetes among people with prediabetes taking metformin is a treatment effect or a preventative effect. They recommend duplicating the effects seen in the present review, then switching both groups to placebo and noting whether the benefit in the intervention group persists.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.