Oral antidiabetic drugs and regression from prediabetes to normoglycemia: a meta-analysis
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CRD summary
The review found that oral hypoglycaemic drugs were associated with increased odds of regression to normoglycaemia in patients with prediabetes. The evidence for a beneficial effect of thiazolidinediones and alpha glucosidase inhibitors was stronger than for biguanides. Limitations of the study quality assessment mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To determine the efficacy of oral antidiabetic drugs in promoting regression from prediabetes to normoglycaemia.

Searching
MEDLINE (1950 to November 2011), EMBASE (1990 to November 2011) and the Cochrane Central Register of Controlled Trials (CENTRAL; to September 2011) were searched, with no language restrictions. Search terms were reported. References lists of identified studies and reviews were manually searched for additional studies.

Study selection
Randomised controlled trials (RCTs) of oral diabetic drugs in patients with prediabetes were eligible for inclusion. Studies had to be at least 12 weeks in duration, and report regression to normoglycaemia. Prediabetes was defined as impaired glucose tolerance, impaired fasting glucose or glycosylated haemoglobin of between 5.7% and 6.7%. Eligible drug classes were thiazolidinediones, biguanides, alpha glucosidase inhibitors, sulphonylureas, meglitinides or dipeptidyl peptidase-4 inhibitors. Eligible comparators were active treatment, no treatment or placebo.

The mean duration of the included studies ranged from 0.25 to five years, and almost all included patients with impaired glucose tolerance. The mean age of participants ranged from 45 to 64 years, and between 12% and 73% were male. Mean BMI ranged from 21 to 34 kg/m², where reported. In most studies, participants received dietary and/or lifestyle advice. The interventions were pioglitazone, voglibose, rosiglitazone, glipizide, acarbose, metformin and troglitazone. Dosages were given in the review. Most studies were placebo-controlled.

Three reviewers independently selected the studies, and disagreements were resolved by discussion.

Assessment of study quality
The Jadad scale was used to assess quality, which scores studies out of five on criteria including randomisation, blinding and description of withdrawals. Scores below 3 were considered of low quality.

Two reviewers independently performed the quality assessment, with discrepancies resolved by discussion.

Data extraction
Data were extracted to calculate odds ratios (OR) and 95% confidence intervals (CI).

Two reviewers independently extracted the data; disagreements were resolved by discussion or a third reviewer.

Methods of synthesis
Results were pooled using a DerSimonian and Laird random-effects meta-analysis. Study heterogeneity was assessed using I². Publication bias was assessed using Egger weighted regression p values. Subgroup analyses were performed on various classes of oral hypoglycaemic drugs. Sensitivity analyses were performed and excluded studies that: did not include any dietary advice or modification; were of low methodological quality; or assessed troglitazone, since this has been removed from sale due to safety concerns.

Results of the review
Thirteen studies were included in the review. Study quality ranged from 1 to 5 on the Jadad scale; four studies were of low quality (Jadad less than 3). The number of participants was not clear due to discrepancies between the table and
text data. It appeared that study size ranged from 18 to 5,269 participants.

Oral hypoglycaemic therapy, compared to placebo/control, was associated with an increase in the odds of regression from prediabetes to normoglycaemia (OR 2.03, 95% CI 1.54 to 2.67; 13 studies, 14 comparisons). There was a high level of heterogeneity (I²=80%). Sensitivity analyses resulted in moderate attenuation of this effect, but a beneficial effect persisted when excluding studies that: did not include any dietary advice or modification (OR 1.91, 95% CI 1.42 to 2.57); were of low methodological quality (OR 1.66, 95% CI 1.21 to 2.29); assessed troglitazone, (OR 1.97, 95% CI 1.47 to 2.65).

Thiazolidinediones (five studies) showed a beneficial effect on regression to normoglycaemia (OR 2.33, 95% CI 1.93 to 2.81), with no evidence of heterogeneity.

Alpha glucosidase inhibitors (four studies) showed a beneficial effect on regression to normoglycaemia (OR 2.02, 95% CI 1.26 to 3.24), with a high level of heterogeneity (I²=81.7%).

The beneficial effect of biguanides (four studies) did not reach pre-defined levels of statistical significance (OR 2.04, 95% CI 0.97 to 4.26), and showed moderate levels of heterogeneity (I²=67.9%).

One study of sulphonylureas did not find an effect on regression to normoglycaemia.

The authors found no evidence of publication bias (p=0.55).

**Authors’ conclusions**

Oral hypoglycaemic drugs were associated with increased odds of regression to normoglycaemia in patients with prediabetes.

**CRD commentary**

The review addressed a clear question. Participant, design, intervention and outcome criteria were specified. The search covered several databases, and search terms were appropriate. No language restrictions were applied to the search, so the results could not be affected by language bias. Steps were taken to reduce errors and bias at all stages of the review process, although some errors in the published paper made it difficult to determine the number of patients on which the review was based. The authors found no evidence of publication bias.

The assessment of study quality used the Jadad scale, which did not address key domains such as allocation concealment and did not evaluate risk of bias. Restricting the results to higher quality studies only partially attenuated the observed results. The risk of bias in the studies included in that analysis was not clear; the use of a random-effects model meant that the small studies may have unduly influenced the pooled effect estimate. The main results were also affected by statistical heterogeneity.

The authors noted that the direction of all individual studies was the same, despite the magnitude of effect differing. They also reported that the main aim of the included trials was to prevent diabetes development, rather than regression to normoglycaemia.

This review was generally well conducted, but limitations of the quality assessment, and the discrepancy between the primary goals of the included trials, and of the review, mean that the reliability of the authors’ conclusions (more specifically, of the pooled effect estimates) is unclear.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more trials of biguanides and sulphonylureas were required to determine their therapeutic effect on regression from prediabetes to normoglycaemia.

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