Lifestyle and medication interventions for the prevention or delay of type 2 diabetes mellitus in prediabetes: a systematic review of randomised controlled trials

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CRD summary
The authors concluded that there was substantial evidence that intensive lifestyle programmes and medications delayed type 2 diabetes mellitus in people with impaired glucose tolerance; which method was more effective remained unclear. The reliability of the conclusions is uncertain given the poor quality and small number of studies included.

Authors' objectives
To assess the effects of lifestyle and pharmacological interventions for the prevention or delay of type 2 diabetes mellitus in prediabetes.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, BIOSIS Previews and LILACS and trial registry databases were searched. Search dates were not reported. No language restrictions were applied. Reference lists relevant meta-analyses were handsearched. Authors of included trials and relevant systematic reviews were contacted to identify unpublished and ongoing studies.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of lifestyle compared to medication interventions and the combination of lifestyle and medication compared to medication or lifestyle alone in individuals with prediabetes were eligible for inclusion. Studies that compared oral hypoglycaemics and anti-obesity agents with lifestyle interventions still on the market were eligible for inclusion. Eligible studies had to follow participants for at least one year. No restriction was applied on criteria for impaired glucose tolerance and impaired fasting glucose.

Primary outcomes were incidence of type 2 diabetes mellitus and normal glucose tolerance. Secondary outcomes included mortality, incidence of cardiovascular disease, morbidity, glycaemic control, plasma lipids, blood pressure, insulin, body weight, adverse effects, compliance and quality of life.

Study settings varied. Lifestyle interventions (content, duration and frequency, delivery personnel) varied and included standard type 2 diabetes mellitus and lifestyle education, instruction on weight reduction via diet and regular exercise, individualised advice on exercise and specific dietary changes. The content, delivery personnel, duration and frequency of included medication (metformin, acarbose) interventions varied. Mean age of participants ranged from 45.2 to 54.6 years. Participants' body mass index (BMI) ranged from 24.8 to 34.0kg/m².

Two reviewers independently assessed studies for inclusion; disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed using The Cochrane Collaboration method for risk of bias assessment. Key criteria assessed included sequence generation, allocation concealment, blinding, completeness of outcome data, potential selective outcome reporting and possibility of other sources of bias (such as early termination of trial).

Two reviewers independently assessed study quality; disagreements were resolved through consensus, author contacts and by involvement of a third reviewer.

Data extraction
Data on number of events and total number of participants were extracted and risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were calculated. Authors were contacted for missing data or where clarification was required.
Two reviewers independently extracted data (primary outcomes only; secondary outcome data were extracted by a single reviewer). Disagreements were resolved through discussion or by contacting the authors of the study.

**Methods of synthesis**

Study results were summarised narratively as there were significant differences in the included interventions. Effect sizes for reported outcomes were presented using forest plots as risk ratios with corresponding 95% CIs.

**Results of the review**

Four RCTs were included (n=5,372 patients, range 178 to 3,234). Overall risk of bias was rated as high. Mean follow-up ranged from 2.5 to 5.0 years.

**Lifestyle versus medication**:
Medication was associated with a positive effect on type 2 diabetes mellitus conversion (RR 1.98, 95% CI 1.03 to 3.80; one study) and no significant difference in effect was found in one study. Medication was associated with a positive effect on reversion to normal glucose tolerance (RR 2.02, 95% CI 1.25 to 3.28; one study).

**Lifestyle and medication versus lifestyle alone**:
Lifestyle alone was associated with a positive effect on type 2 diabetes mellitus conversion (RR 1.48, 95% CI 1.23 to 1.78; one study). Lifestyle and medication was associated with positive effects (RR 0.75, 95% CI 0.64 to 0.87 and RR 0.79, 95% CI 0.69 to 0.91; two studies). A single study found no significant difference in effects.

**Lifestyle and medication versus lifestyle alone**:
A single study found no significant difference in effects on reversion to normal glucose tolerance.

**Lifestyle and medication versus medication alone**:
A single study found no significant difference in effects on type 2 diabetes mellitus conversion.

**Cost information**

One survey reported that individuals at risk of type 2 diabetes mellitus were reluctant to pay for a programme similar to the Indian Diabetes Prevention Programme Intensive Lifestyle intervention with US$65 out-of-pocket costs per month.

**Authors’ conclusions**

There was substantial evidence that intensive lifestyle programmes and medications delayed type 2 diabetes mellitus in people with impaired glucose tolerance; which method was more effective remained unclear.

**CRD commentary**

The review question was clearly stated. Several relevant databases were searched. Attempts were made to search for unpublished studies. Review processes were done in duplicate, which minimised risks of error and bias. Study quality was assessed using appropriate criteria; overall quality was reported to be poor. The decision to combine results narratively was justified given significant differences in the included interventions. Overall, few studies with limited sample sizes were included.

The reliability of the authors' conclusions is uncertain given the poor quality and small number of studies included.

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

**Practice**:
The authors stated that there was insufficient evidence to make recommendations on the choice between lifestyle and medication and for lifestyle and medication against a lifestyle or medication intervention alone. They stated that the decision on whether to implement a lifestyle intervention or begin medication in patients with impaired glucose tolerance to delay type 2 diabetes mellitus should be guided by the balance between the advantages and side-effects of each method and incorporate patients’ values.

**Research**:
The authors stated that further RCTs were needed on more intensive lifestyle modification and incorporation of measures to maximise compliance. Future RCTs should include post-intervention follow-up periods and measure and
report glucose outcomes on a continuous scale as well as progression to type 2 diabetes mellitus and normal glucose tolerance.

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