Clinical effect of metformin in children and adolescents with type 2 diabetes mellitus: a systematic review and meta-analysis

Al-Shareef MA, Sanneh AF, Aljoudi AS

CRD summary
This review concluded that there was limited and unconvincing evidence to suggest that metformin can improve glycaemic control in children and adolescents with type 2 diabetes. These conclusions and the authors' recommendations for further research appear justified and reliable.

Authors' objectives
To assess the clinical effectiveness of metformin monotherapy versus other treatments for type 2 diabetes in children and adolescents.

Searching
The Cochrane Library, MEDLINE, EMBASE and IPA were searched up to May 2008 with no language restrictions. Four clinical trial registers were searched (named in the paper). American Diabetes Association and Diabetes UK websites were scanned for abstracts of recent meetings. Reference lists of included studies, systematic reviews, meta-analyses and health technology assessment reports were handsearched. Publishers of relevant trials and experts were contacted to locate further studies.

Study selection
Randomised controlled trials comparing the clinical effectiveness of metformin monotherapy (extended or immediate release) versus other treatments of type 2 diabetes in children (aged two to 12 years) or adolescents (aged 12 to 18 years) were eligible for inclusion. Primary outcomes of interest included glycaemic control indicated by glycosylated haemoglobin (HbA1c) levels, diabetes-related complications and adverse effects. Studies with less than four weeks of exposure to treatments were excluded.

The mean age of participants in all of the included trial arms was 14 years. Mean HbA1c levels at baseline ranged from 8.3 to 9 and for fasting blood plasma glucose ranged from 9.2 to 172. Weight ranged from 83kg to 93kg. Body mass index (kg/m²) ranged from 32 to 34.

Two reviewers independently selected studies for inclusion; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed trial quality using a checklist from the National Institute of Health Research Centre for Reviews and Dissemination (NIHR CRD). Criteria included randomisation, allocation concealment, blinding and use of intention to treat analysis. Trials were assessed as good quality (all criteria met), moderate quality (one or more of the criteria partially met) or poor quality (one or more criteria not met). Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data on the outcomes (which included mean changes in HbA1c levels and body mass index from baseline and number of adverse events) to enable calculation of mean differences, risk ratios and corresponding 95% confidence intervals. Study authors were contacted for any missing information.

Methods of synthesis
Effect estimates and their 95% confidence intervals were pooled using random-effects models. Statistical heterogeneity were assessed using the $X^2$ test and the $I^2$ statistic ($I^2>50\%$ indicated substantial heterogeneity). Other outcomes were synthesised narratively.

Results of the review
Two randomised controlled trials (both completed, sample sizes of 263 and 84) were included in the review and meta-
analyses. The quality of the two trials was poor and they were at high risk of bias; a breakdown of the results was provided. One control group received placebo and the other received glimepiride.

The trial with the glimepiride control group reported significant reductions in mean change in HbA1c from baseline for both the metformin (-0.71%, p=0.0002) and glimepiride arms (-0.54%, p=0.001).

The placebo-controlled trial found a statistically significant greater reduction of HbA1c from baseline with metformin compared with control (MD -1.10, 95% CI -1.19 to -1.01). This trial also demonstrated a significant reduction in fasting plasma glucose with metformin (-42.9mg/dL) over the placebo control (+21.4mg/dL) with a mean difference of -64.80 in favour of metformin. A significant decrease in low-density lipoprotein levels was reported for the metformin group (data not shown).

Meta-analyses of the two trials showed that there were no statistically significant differences between metformin and control groups for mean changes in HbA1c from baseline (MD -0.63%, 95% CI -1.56 to 0.30; \(I^2=99\%\)) and mean changes in body mass index from baseline (MD -0.46, 95% CI -2.27 to 1.34; \(I^2=0\%\)).

Further results for each trial were reported separately in the review; this included adverse event results from three additional retrospective cohort studies. The authors did not consider any of these data amenable to meta-analysis.

**Authors’ conclusions**

There was limited and unconvincing evidence to suggest that metformin can improve glycaemic control in children and adolescents with type 2 diabetes compared with other interventions.

**CRD commentary**

The review question and inclusion criteria were clearly defined, although additional adverse event results were reported from trials that did not meet the inclusion criteria. Extensive efforts were taken to identify relevant studies in published, unpublished and grey literature. No language restrictions were applied. The searches were only up to 2008 and more recent studies may have been missed; this included ongoing studies, whose results may only have become available after the searches were performed.

Review processes were performed in duplicate so risks of reviewer error and bias were minimal. Suitable quality assessment criteria were employed and showed that both included trials were of poor quality. The primary use of a narrative method of synthesis and the authors’ focus on these results was appropriate given the limitations of the small evidence base. The authors acknowledged that the small number of trials included, differences between the trials, their short durations and their poor quality were major limitations of the review.

The authors’ conclusions and recommendations for further research appear justified and reliable.

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

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

**Research:** The authors stated that a large adequately powered multicentre randomised controlled trial with double blinding was required to further assess the efficacy of metformin monotherapy and its impact on adverse events and quality of life in children and adolescents.

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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.