INPLASY

Metformin for the prevention of progression of prediabetes to type 2 diabetes: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No external financial support was sought.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 January 2024 and was last updated on 12 January 2024.

INTRODUCTION

*R*eview question / Objective P = Patients with pre-diabetes ; I = Metformin; C = Lifestyle modification; O = Progression to T2D.

Rationale The predominant strategy used to prevent the transition from pre-diabetes to T2DM has been lifestyle modification aiming at weight loss and reduction in insulin resistance. However, achieving a required 5% weight loss from baseline for metabolic benefits are difficult to achieve and more importantly to sustain. A mean weight loss of 6.5 kg from baseline in the diabetes prevention program (U.S. DPP) contrasts with the analysis of Davies et al, where the mean weight loss was a non-significant 0.27 kg. In view of this heterogeneity of outcomes certain medicines capable of inducing weight loss and improving insulin resistance (biguanides and thiazolidinediones) had been investigated. Metformin stands out as the most promising agent in view of its effect on weight and insulin resistance as well as a positive risk-benefit-cost effectiveness ratio.

This meta-analysis was undertaken to explore the effectiveness of metformin in preventing the progression to T2D taking into account the inherent heterogeneity of the studies, and re-analysing the data having removed the significant outliers.

Condition being studied Prediabetes.

METHODS

Search strategy Randomized prospective studies identified through a thorough database search (Cochrane Library) will be included for analysis.

The search will be divided into two categories, (a) related to the intervention in question, and (b) related to the primary disease in question. The search terms will be combined using the Booleans "OR" and "AND". The terms included (a) "Prediabetic state" OR "Glucose intolerance" OR "Impaired fasting glucose" OR "IFG" OR "Impaired glucose tolerance" OR "IGT", AND (b) "Metformin". The primary filters to be included are human subjects and trials, thereby excluding review articles, and conference abstracts. Subsequently, duplicate citations will be tracked and removed with the final step of screening being non-adherence to the pre-specified inclusion criteria.

Participant or population Prediabetes patients above 18 years of age and a minimum of 6 weeks follow up.

Intervention Metformin.

Comparator Lifestyle intervention.

Study designs to be included Random effects model meta-analysis with subgroup and meta-regression analysis faced with significant heterogeneity.

Eligibility criteria • Randomised prospective studies.• Studies reporting pre-diabetes in the standardized format including IFG and IGT.• Metformin as the primary intervention arm.• Lifestyle modification as the standard of therapy in the comparative arm. • Age above 18 years.• A minimum follow- up period of 6 weeks.

Information sources Citations identified by a Cochrane library search freely available on the web.

Main outcome(s) Prevention of conversion of prediabetes to Type 2 diabetes.

Quality assessment / Risk of bias analysis Cochrane risk of bias algorithm.

Strategy of data synthesis 1. Random effects model meta-analysis using risk ratio (RR) as the effect size. 2. Confidence interval (95%) will be used tom assess the precision of the effect size estimate. 3. Prediction interval will be used to identify heterogeneity of the effect size.

Subgroup analysis The impact of the different doses of metformin used in the different studies on the outcome.

Sensitivity analysis Leave-one-out sensitivity analysis will be performed to identify any citation skewing the overall outcome.

Language restriction English language.

Country(ies) involved India.

Keywords Pre-diabetes, T2D, meta-analysis, metformin, LSM.

Contributions of each author
Author 1 - Krishna Seshadri - Conceptualised the manuscript and plan to contribute to literature search including writing the manuscript.
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Author 2 - Samit Ghosal - Plan to performed the meta-analysis and contribute to literature search including writing the manuscript.
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