INPLASY PROTOCOL

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None declared.

Association of Bisphosphonates with Risk of Incident Diabetes and Glycemic Control: A Protocol of Systematic Review and Meta-analysis

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Review question / Objective: **To determine the association between bisphosphonate use and the risk of incident diabetes and glycemic control in adults with updated evidence from clinical trials and observational studies.**
Eligibility criteria: **The inclusion criteria for studies assessing risk of incident diabetes are as follows: (1) availability of data on bisphosphonate use in individuals without diabetes; (2) evaluation of the risk of diabetes for bisphosphonate users compared with controls; and (3) either clinical trials or observational studies. To assess effects of bisphosphonates on glycemic control, we will include studies with: (1) availability of data on bisphosphonate use in individuals regardless of diabetes state; (2) evaluation of the glycemic parameters, including fasting blood glucose (FBG) or glycosylated hemoglobin (HbA1c), for bisphosphonate users compared with controls; (3) report sufficient data on the change in glycemic parameters (FBG and HbA1c) before and after bisphosphonate use or placebo/comparison use; (4) either clinical trials or observational studies. We will exclude studies with only a single arm without comparison.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 April 2022 and was last updated on 20 April 2022 (registration number INPLASY202240125).

INTRODUCTION

Review question / Objective: **To determine the association between bisphosphonate use and the risk of incident diabetes and glycemic control in adults with updated evidence from clinical trials and observational studies.**

Condition being studied: **Some studies have indicated that bisphosphonates may reduce the risk of incident diabetes and**

improve glycemic control. However, current literature is inconsistent and inconclusive to determine if the effect exists.

METHODS

Search strategy: We will use terms related to "bisphosphonate" and "diabetes mellitus" to search through Medline, Embase, and Cochrane library databases.

Participant or population: Adults eligible for bisphosphonate use.

Intervention: Bisphosphonate use.

Comparator: Placebo, other anti-osteoporosis drugs, or no bisphosphonate use.

Study designs to be included: Clinical trials, cohort studies, or case-controlled studies.

Eligibility criteria: The inclusion criteria for studies assessing risk of incident diabetes are as follows: (1) availability of data on bisphosphonate use in individuals without diabetes; (2) evaluation of the risk of diabetes for bisphosphonate users compared with controls; and (3) either clinical trials or observational studies. To assess effects of bisphosphonates on glycemic control, we will include studies with: (1) availability of data on bisphosphonate use in individuals regardless of diabetes state; (2) evaluation of the glycemic parameters, including fasting blood glucose (FBG) or glycosylated hemoglobin (HbA1c), for bisphosphonate users compared with controls; (3) report sufficient data on the change in glycemic parameters (FBG and HbA1c) before and after bisphosphonate use or placebo/comparison use; (4) either clinical trials or observational studies. We will exclude studies with only a single arm without comparison.

Information sources: MEDLINE, Embase, and Cochrane library.

Main outcome(s): (1) relative risk of incident diabetes of bisphosphonates users compared to controls, (2) difference in fasting blood glucose change between bisphosphonate users and controls, (3) difference in HbA1c change between bisphosphonate users and controls.

Quality assessment / Risk of bias analysis: Two reviewers will independently evaluate the quality of included studies using the Cochrane Risk of Bias Assessment Tool for randomized controlled trials and the Newcastle-Ottawa Scale for non-randomized studies. To achieve consensus, a third reviewer will resolve discrepancies in the data extraction and quality assessment.

Strategy of data synthesis: We will calculate the pooled RRs and weighted mean difference (WMD) with 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects model. We will use unadjusted results for RCTs and adjusted data for non-randomized studies. The relative risks (RRs) and odds ratios (ORs) obtained from clinical trials and observational studies will be pooled together since the values of ORs would be close to those of RRs if the endpoint occurs relatively infrequently.

Subgroup analysis: We will perform subgroup analyses and meta-regression to assess the possible effect modulators and explore the source of heterogeneity. Subgroup analyses will include age, sex, obesity, study design, and types of bisphosphonates used.

Sensitivity analysis: Leave-one-out sensitivity analyses will be performed by omitting each study, each at a time, to evaluate the influence of every single study on the overall pooled estimates.

Language: No language limit will be applied.

Country(ies) involved: Taiwan.

Keywords: Bisphosphonates; Diabetes mellitus; Glycemic control; Osteoporosis; Systematic review; Meta-analysis.

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