Risk factors for hyperglycemia and hypoglycemia in adults with pharmacologically treated type 2 diabetes mellitus: a quantitative systematic review protocol

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ABSTRACT

Objective: The objective of this review is to identify and synthesize the risk factors for hyperglycemia or hypoglycemia in adults with pharmacologically treated type 2 diabetes mellitus in any scenarios and environments for health care.

Introduction: Studies around the world have investigated which factors are associated with episodes of alteration of blood glucose level. It is through the characterization of these factors that nurses can plan and intervene accurately in the control of serum glucose levels in people with diabetes.

Inclusion criteria: This review will include studies conducted among adults with pharmacologically treated type 2 diabetes mellitus in any scenarios and environments for health care. Studies should focus on risk factors for the variation of fasting glycemic levels lower than 3.9 mmol/L and higher than 7.21 mmol/L, as well as postprandial glycemic levels lower than 3.9 mmol/L and higher than 10 mmol/L.

Methods: Databases to be searched include MEDLINE, Embase, CINAHL, PsycINFO, Web of Science, Scopus, LILACS, and ScienceDirect. Following the search, titles and abstracts will be screened by two independent reviewers for assessment against the inclusion criteria for the review. The full text of selected citations will be assessed in detail against the inclusion criteria, and studies selected for retrieval will be assessed by two independent reviewers for methodological validity using JBI critical appraisal tools. Studies will not be excluded based on their quality assessment. Data will be extracted using the standardized data extraction tools. Quantitative data will, where possible, be pooled in statistical meta-analysis.

Systematic review registration number: PROSPERO (CRD42019134755)

Keywords: diabetes mellitus; glycemic variability; hyperglycemia; hypoglycemia; risk factors

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Introduction

Diabetes mellitus, a complex metabolic disorder characterized by blood sugar and insulin dysregulation,[1,2] has an estimated global prevalence of more than 425 million people, and the number of people with the disease is set to rise to 629 million in 2045.[3] This will impose a substantial burden on patients, caregivers, health systems, and the economy.[4] Diabetes mellitus requires continuous medical care with multifactorial risk-reduction strategies beyond glycemic control.[5]

People with well-controlled diabetes can live long and healthy lives with interprofessional management emphasizing optimal, individualized care.[6] However, this reality can be a challenge for people with diabetes and their families. The ineffective management of glycemia may result in hyperglycemia or hypoglycemia, and the maintenance of these conditions can result in multiple health complications. In

patients with diabetes, hyperglycemia is the sum of the fasting and postprandial elevation in blood glucose.[7] The preprandial versus postprandial patient self-monitoring of blood glucose targets is a complex issue.[5] Currently, the glycemic recommendation of the American Diabetes Association (ADA) for pre-meal glucose target in nonpregnant adults with diabetes is 80 to 130 mg/dL (4.4 to 7.2 mmol/L), and postprandial plasma glucose target one to two hours after the start of a meal is 180 mg/dL (10.0 mmol/L).[5] Hypoglycemia is the sum of the fasting and postprandial decrease in blood glucose, and because many people with diabetes demonstrate impaired counter-regulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level < 70 mg/dL (3.9 mmol/L) is considered clinically important, independent of the severity of acute hypoglycemic symptoms.[5]

Most observational studies have found that hyperglycemia and hypoglycemia result in severe complications: adverse outcomes in patients receiving critical care[8-10]; risk of developing pancreatic ductal adenocarcinoma,[11] one of the leading causes of organ failure[6]; major risk factors for dementia[12-14]; increased risk of hospitalization and unplanned readmission[15-18]; as well as increased costs, hospital length of stay, and mortality and morbidity attributable to cardiovascular, cerebrovascular, and fall events.[19,20]

Within nursing practice, it is critical to identify relevant causal factors, independently modified by a professional nurse, and associated conditions not independently modified by a professional nurse. The nursing diagnosis of risk for unstable blood glucose level contributes to the management of diabetes and minimizes the chances of complications for patients and families.

A risk factor refers to "any attribute, characteristic, or exposure of an individual, which increases the likelihood of developing a noncommunicable disease."[21(p.3)] As a component of the nursing diagnosis, risk factors are "environmental factors and physiological, psychological, genetic, or chemical elements that increase the vulnerability of an individual, family group, or community to an unhealthy event."[22(p.39)] In clinical judgment, risk factors are essential elements contributing to an accurate diagnosis. A nursing diagnosis of risk is a clinical judgment concerning the susceptibility for developing an undesirable response to health conditions or life processes.[22]

It is through the characterization of these factors that nurses can plan and intervene accurately in the control of serum glucose levels in people with or without diabetes. The nursing diagnosis "risk for unstable blood glucose level" reveals the susceptibility to variation in serum glucose levels in relation to the normal range that can compromise health.[22] Through this diagnosis, it is possible to predict the susceptibility for people with diabetes to experience hyperglycemia or hypoglycemia, which may reveal the inadequate control of the glycemia, the lack of adherence to the therapeutic regimen, or the difficulty in changing life habits. However, according to the NANDA International Nursing Diagnoses, the risk for unstable blood glucose level is a nursing diagnosis with a level of evidence of 2.1, demanding a concept analysis.[22] A systematic literature review is recommended to identify and synthesize risk factors for hyperglycemia or hypoglycemia in adults with type 2 diabetes mellitus (T2DM) in continuous drug therapy. The results could contribute to important information and evidence for clinicians and nurses, and the refinement of nursing knowledge.

Studies around the world have explored which factors are associated with episodes of alteration of blood glucose level. A nationwide, population-based cohort study developed in South Korea with patients with T2DM found that several indicators could independently predict an increased risk of severe hypoglycemia.[23] These patients were older, female, had been managing diabetes for a prolonged period, had a low body mass index used insulin or multiple classes of glucose-lowering medications, smoked, drank alcohol, did not exercise, exhibited hypertension or chronic kidney disease, and had a history of severe hypoglycemia, multiple comorbidities, and low or high glucose levels. A multicenter, cross-sectional survey of Muslim patients with diabetes investigated Ramadan fasting and found that the hypoglycemia group were significantly younger; patients with hypoglycemia had been diabetic for a significantly longer period; and patients with type 1 diabetes mellitus had a higher risk of hypoglycemia.[24] A retrospective observational study conducted in an outpatient clinic in northern Taiwan investigated the changes in blood sugar in patients with T2DM when traveling abroad. The results showed that the hypoglycemic episodes were associated with the number of times the patients had crossed time zones.[23]

A preliminary search was conducted in PROS-PERO, MEDLINE, Cochrane Database of Systematic Reviews, and the *JBI Database of Systematic Reviews and Implementation Reports,* and no current or in-progress systematic reviews on the topic were identified. The objective of this review is to identify and synthesize the exposures for hyperglycemia or hypoglycemia in adults with pharmacologically treated T2DM in any scenarios and environments for health care.

Review question

What are the exposures associated with hyperglycemia and hypoglycemia in adults with pharmacologically treated T2DM in any scenarios and environments for health care?

Inclusion criteria
Participants

This review will include studies of adults (18 to 64 years old) with pharmacologically treated T2DM in any scenario and environment for health care. Studies conducted with adults with T2DM at the start of treatment or in the evaluation of new drug treatments will not be included. Studies with adult participants with T2DM using oral antidiabetic agents such as biguanides, sulphonylureas, meglitinides, glitazones, alfaglasse inhibitors, gliptins, SGLT2 inhibitors, and/or insulins that are ultra-fast acting (glulisine, lipro, asparte), fast (human insulin regular), intermediate (human NPH), long duration (glargine, determir, degludeca), and pre-mixed will be included. Studies with participants using continuous insulin infusion systems will not be considered, nor will studies that only evaluate older adults.

Exposure of interest

This review will include studies that focus on risk factors for the variation of fasting and postprandial glycemic levels. Potential exposures such as age, sex, race, education, impaired awareness, intensive glucose control, duration of diabetes, learning problems, body mass index, use of insulin or multiple classes of glucose-lowering medications, smoking, drinking, lack of exercise, presence of hypertension, renal disease, depression, previous severe hypoglycemia history, multiple comorbidities, cultural practices, and food insecurity, among others, will be considered.

Outcomes

This review will consider studies that include the following outcomes in adults with pharmacologically treated T2DM: risk factors associated with the variation of fasting glycemic levels lower than 70 mg/dL (3.9 mmol/L) and higher than 130 mg/dL (7.21 mmol/L), or postprandial glycemic levels lower than 70 mg/dL (3.9 mmol/L) and higher than 180 mg/dL (10 mmol/L) one to two hours after the start of a meal. The definitions were included according to ADA-recommended, pre-meal glucose targets and postprandial plasma glucose one to two hours after the start of a meal.[5] These outcomes will be measured by a capillary glycemia test or blood test of fasting or postprandial glycemia in serum, gel, dry serum, or fluoride tubes analyzed by enzymatic methods. This review will include studies that evaluate the peak postprandial capillary plasma glucose, but no post-overload glycemic check results will be included. Also, all studies that report the outcomes not specifically based on the ADA definition, or studies that used other appropriate definitions, will be included with a sensitivity analysis of their evidence conducted.

Types of studies

This review will consider longitudinal study designs including cohort retrospective or prospective, and case-control. In addition, analytical cross-sectional studies, in which the author makes explicit that a dependent variable was hyperglycemia or hypoglycemia, will be considered for inclusion.

Methods

The proposed systematic review will be conducted in accordance with JBI methodology for systematic reviews of etiology and risk.[25] The protocol has been registered in PROSPERO: CRD42019134755.

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE and CINAHL using "hyperglycemia" and "hypoglycemia" was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (PubMed) (see Appendix I). The search strategy,

including all identified keywords and index terms, will be adapted for each included information source.

The following databases will be included in the search strategy: MEDLINE (PubMed; 1946–present), Embase (OvidSP; 1883–present), CINAHL (EBSCO; 1961–present), PsycINFO (OvidSP; 1860–present), Web of Science (1900–present), Scopus (1960–present), Literature of the Latin American and Caribbean Health Sciences (LILACS; 1982–present), and ScienceDirect (1997–present). The search strategy, to be used in MEDLINE (PubMed), is detailed in Appendix I. This search strategy will be adapted for other databases, in consultation with an information specialist/librarian. The search for unpublished studies will include EThOS, OpenGrey, ProQuest Dissertations and Theses, CAPES Thesis and Dissertations Catalog, MedNar, Google Scholar, Open Access Theses And Dissertations (OATD), Open Access Scientific Repositories of Portugal (RCAAP), and DART-Europe E-theses Portal (DART-E). The reference lists of any identified reviews and primary studies included will be screened for additional studies.

Studies published in any language will be included. Translations will be performed when necessary. All the studies in the database from its inception to the present date will be considered

Study selection

Following the search, all identified citations will be collected and uploaded into Mendeley (Mendeley Ltd., Elsevier, Netherlands) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[26] The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[27]

Assessment of methodological quality

Studies selected for retrieval will be assessed independently by the primary and the secondary reviewers for methodological validity using JBI critical appraisal tools for cohort studies, case-control studies, and analytical cross-sectional studies.[25] Any disagreements between the reviewers at each stage will be resolved through discussion or with a third reviewer. All studies, regardless of their methodological quality, will undergo data extraction and synthesis where possible. The number of papers included and excluded at each stage and the main reason for exclusion will be recorded in a flow diagram. All searches, decisions, and steps will be documented and archived by the primary reviewer. The results of the critical appraisal will be reported in narrative form and in a table.

Data extraction

Data will be extracted from papers included in the review by two independent reviewers using the standardized data extraction tools in JBI SUMARI. The data extracted will include specific details about study methods, populations, type, different categories of exposure of interest, outcomes, and results of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis

Quantitative data will, where possible, be pooled in a random-effects meta-analysis model using JBI SUMARI.[26,28] All results will be subject to double data entry. Effect sizes will be expressed as odds ratio or risk ratios for categorical data and as Hedges' g statistic, the weighted mean difference, for continuous data. The 95% confidence intervals of the effect sizes will be estimated. For case-control studies, raw data will be used to estimate crude odds ratio with 95% confidence interval, and for other designs, raw data will be used to estimate crude risk ratios with 95% confidence interval, where possible. All studies will be pooled to estimate an adjusted relative risk

with 95% confidence intervals, irrespective of the study design used and the binary effect measure used. When statistical pooling is not possible, the findings will be presented in a narrative form, including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated to assess publication bias. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.[29,30] Heterogeneity will be explored using a test that examines the null hypothesis that "all studies are evaluating the same effect."[31(p.557)] Cochran's Q will be computed by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner as in the meta-analysis. P values are obtained by comparing the statistic Cochran's Q with a χ^2 distribution with k-1 degrees of freedom (where k is the number of studies); a cut-off of 10% for significance will be applied, as recommended by Hedges.[32] To quantify the effect of heterogeneity, a measure of the degree of inconsistency I^2 will be used. This measure describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[31] For this study, the decision rule for considering high and significant heterogeneity will be: P value ≤ 0.10 for Q and an $I^2 > 50\%$. To calculate the weighted means of the studies' results, a fixed-effects model will be used if the heterogeneity is not significant, and a random-effects model will be adopted if there is significant heterogeneity. To examine the influence of each study on the overall results, a sensitivity analysis, omitting one study at a time, will be performed to explore potential sources of heterogeneity and test the stability of pooled results.

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Appendix I: Search strategy

MEDLINE (PubMed)
Search conducted August 18, 2020.

Query	Search	Records retrieved
#1	''Diabetes Mellitus, Type 2''[Mesh] OR ''Diabetes Mellitus, Type 2''[tw] OR ''type 2 diabetes mellitus''[tw] OR ''type two diabetes mellitus''[tw]	151,010
#2	''Hyperglycemia''[Mesh] OR ''Hyperglycemia''[tw] OR hyperglycaemia[tw] OR ''Hypoglycemia''[Mesh] OR ''Hypoglycemia''[tw] OR ''Hypoglycaemia''[tw]	114,667
#3	(''Diabetes Mellitus, Type 2''[Mesh] OR ''Diabetes Mellitus, Type 2''[tw] OR ''type 2 diabetes mellitus''[tw] OR ''type two diabetes mellitus''[tw]) AND (''Hyperglyce-mia''[Mesh] OR ''Hyperglycemia''[tw] OR hyperglycaemia[tw] OR ''Hypoglycemia'' [Mesh] OR ''Hypoglycemia''[tw] OR ''Hypoglycaemia''[tw])	21,726
#4	''hypoglycemic agents''[MeSH] OR ''antidiabetic drugs''[tw] OR ''antidiabetic agents''[tw]	71,899
#5	(''Diabetes Mellitus, Type 2''[Mesh] OR ''Diabetes Mellitus, Type 2''[tw] OR ''type 2 diabetes mellitus''[tw] OR ''type two diabetes mellitus''[tw]) AND (''Hyperglyce-mia''[Mesh] OR ''Hyperglycemia''[tw] OR hyperglycaemia[tw] OR ''Hypoglycemia'' [Mesh] OR ''Hypoglycemia''[tw] OR ''Hypoglycaemia''[tw]) AND (''hypoglycemic agents''[MeSH] OR ''antidiabetic drugs''[tw] OR ''antidiabetic agents''[tw])	8158