



BMJ Open Association between insulin resistance and post-ischaemic stroke outcome in patients without diabetes: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Insulin resistance is an independent risk factor for atherosclerosis, coronary artery disease and ischaemic stroke. Currently, insulin resistance is not usually included in post-stroke risk stratification. This systematic review and meta-analysis intends to determine if available scientific knowledge supports an association between insulin resistance and post-stroke outcomes in patients without diabetes.

Methods and analysis The authors will conduct a literature search in Medline, Embase, Web of Science and Cochrane Central. The review will include studies that assess the association between elevated insulin homeostasis model of insulin resistance (HOMA-IR) and post-stroke outcome (functional outcome and recurrent stroke). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines will be used. The primary outcome will be post-stroke functional outcome (Modified Rankin Scale), and the secondary outcome will be recurrent ischaemic stroke. Comparison of outcome will be made between highest and lowest HOMA-IR range (as defined in each article included in this systematic review). Risk of bias will be assessed qualitatively. Meta-analysis will be performed if sufficient homogeneity exists between studies. Heterogeneity of outcomes will be assessed by I^2 .

Ethics and dissemination No human or animal subjects or samples were/will be used. The results will be published in a peer-reviewed journal, and will be disseminated at local and international neurology conferences.

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INTRODUCTION

Patients with ischaemic stroke or transient ischaemic attack (TIA) have a 20% chance of recurrence within 5 years.^{1–3} Type 2 diabetes mellitus (T2DM) is an important independent risk factor in stroke recurrence and post-stroke disability.^{4–6} The gold standard diagnostic test for T2DM is the glycosylated haemoglobin A1c (HbA1c) (>6.5% diagnostic of T2DM). It is simple, cost-effective and internationally validated.^{7–9}

Strengths and limitations of this study

- This is a novel systematic review/meta-analysis.
- There will likely not be many studies that meet protocol requirements.
- Lack of homogeneity in homeostatic model assessment of insulin resistance reporting could hinder data synthesis.

T2DM arises from long-standing clinically unrecognised insulin resistance.¹⁰ The gradual rise in insulin resistance leads to hyperinsulinaemia, which is associated with intima-media thickening, atherosclerosis and compromised stability of the extra and intracranial vasculature.^{11–13} Clinically, insulin resistance is associated with hypertension, dyslipidaemia and hypercoagulability and is an independent risk factor for increased mortality and incident cardiovascular events (myocardial infarction (MI) and stroke).^{14–18} Despite the established importance of insulin resistance in cardiovascular and cerebrovascular disease, there is a paucity of evidence linking insulin resistance with ischaemic stroke outcomes.¹⁹

Some work to manage post-stroke insulin resistance has been performed. The Insulin Resistance in Ischaemic Stroke (IRIS) trial showed benefit for pioglitazone, a thiazolidinedione-type peroxisome proliferator-activated receptor gamma agonist that increases insulin sensitivity, in that it was associated with reduced recurrent stroke or MI.^{20–21} However, the glitazone drug class is associated with increased risk of bladder cancer, heart failure and osteoporosis, and thus has not been approved for secondary prevention of stroke.²² Importantly, the results of the IRIS trial provide proof of concept that insulin resistance may play a role in post stroke functional outcomes.

Screening for insulin resistance in patients with stroke is not routinely performed, due in part to the lack of clinical consensus regarding screening tools. The HbA1c is not a direct measure of insulin resistance, and only correlates with stroke in the diabetic range ($>6.5\%$).²³ The homeostatic model assessment of insulin resistance (HOMA-IR) is, by contrast, a direct measure of insulin resistance. It is a validated scale of insulin resistance commonly used in clinical research.²⁴ This direct measure of insulin resistance is derived from fasting serum insulin and glucose levels ($(\text{fasting insulin} \times \text{fasting glucose}) / 22.5$). Originally proposed in 1985, it has shown comparable results with the euglycemic hyperinsulinaemic clamp, the gold-standard measure of insulin resistance.^{24 25} The HOMA-IR is less invasive, simpler to interpret and cheaper than the euglycemic clamp.²⁶

A non-systematic literature search identified four observational cohort studies that associated HOMA-IR with post-stroke outcomes (disability/mortality) and recurrent ischaemic stroke (or TIA).^{27–30} There is, however, no systematic review or meta-analysis to collate these results and help guide the use of the HOMA-IR as a predictive tool in patients with ischaemic stroke.

The purpose of this protocol paper is to describe how we will conduct a systematic review of the available literature to answer the following question: among patients without diabetes with ischaemic stroke or TIA, is insulin resistance, as measured by the HOMA-IR, associated with (1) worse functional outcome as measured by the Modified Rankin Scale (mRS 3–6) or (2) increased risk of stroke recurrence?

METHODS

The protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) guidelines.³¹ The PRISMA-P checklist was used to indicate adherence to the guidelines (online supplemental file 1). Categories that do not apply are marked non-applicable (N/A). In the case of an amendment, the date and the specifics about the amendment will be recorded in the systematic review, and will be reported through the PROSPERO database.

The authors plan to follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in all areas that they are applicable, in the conduction of the systematic review and meta-analysis.^{32 33} There was no involvement of patients in this protocol paper.

Eligibility criteria

Cohort studies will be eligible to be included. Case studies, case series and cross-sectional studies will not be included. We have decided to focus only on cohort studies, with the goal of a more homogeneous resultant population. We have also chosen to exclude interventional studies so that there is no confounding of an intervention modifying the post-stroke recovery, and diluting the proposed outcome associations.

The population studied must be adults (age >18 years old) who have had an incident ischaemic stroke or TIA. Comparison should be made between patients in the upper range of HOMA-IR (exposed) and those in the lower range of HOMA-IR (comparator). There is no established HOMA-IR threshold for elevated insulin resistance. The upper and lower ranges of HOMA-IR will likely vary in articles included in this systematic review. Outcome measures should include post-stroke functional outcome (preferably by mRS) and stroke recurrence.

In order to be eligible, studies must include the fasting plasma glucose (FPG) and or the HbA1c values for individuals, to identify patients without diabetes ($\text{HbA1c} < 6.5\%$ or $\text{FPG} < 7 \text{ mmol/L}$). Only patients without diabetes from relevant studies will be included in meta-analysis. There will not be any date range restrictions. Only abstracts and articles available in English will be eligible.

Search strategy

Search criteria

1. “Insulin resistance” AND “ischemic stroke”.
2. Observational studies (cohort and case-control).
3. Experimental studies (RCTs).
4. Case reports/series.
5. Interventional studies.
6. Human studies.
7. Original articles in English.
8. No commentaries, letters and responses.

A search strategy, based on the above search criteria, has been designed in collaboration with an experienced librarian (online supplemental file 2). The librarian will conduct a preliminary search to confirm the accuracy of the search strategy to identify observational studies that fit the description above. The search will be performed after acceptance of this protocol article. The search strategy will then be peer-reviewed by a second librarian. It will then be used to search four databases of peer-reviewed medical publications: Medline (Ovid), Embase, Web of Science, EBM Reviews and Cochrane Central Register of Controlled Trials (CENTRAL). Prior to submission of the systematic review and meta-analysis, a follow-up literature search will be performed to determine whether new data have been released since the initial search was performed.

Study records

Study selection

The records will be managed by use of Covidence software. Search criteria have been created in coordination with an experienced librarian who will perform the search for articles fitting the inclusion criteria. The selected articles will be placed in Covidence. Two authors will independently review the titles and abstracts of the articles. Articles will be chosen for full review and inclusion in the review based on consensus between the two reviewers. Furthermore, the references of chosen articles will be searched for any articles that fit criteria. Any lack of consensus will be adjudicated with the participation of the senior author. Authors will report reasons for

Table 1 Data collection items

Domain	Data items
Study characteristics	Study ID, year of publication, type of study, country of study
Population demographics	Stroke severity (NIHSS), type of stroke (TOAST classification), acute stroke interventions (tPA, EVT), mRS prior to stroke
Population biochemical data	Mean HbA1c, mean FPG, HOMA-IR, statistical tools for quantile calculation
Outcome measures	Follow-up interval, functional outcome (mRS), stroke recurrence
Risk of bias assessment	Population selection, comparability of exposed/non-exposed groups, outcome measures (assessment, reliability, comparability), medications (prior and post stroke), outcome assessor blinding, follow-up attrition rate, reporting bias assessment

EVT, endovascular thrombectomy; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; mRS, Modified Rankin Scale; NIHSS, NIH Stroke Scale; TOAST, Trial of ORG 10172 in acute stroke treatment; tPA, tissue plasminogen activator.

exclusion of each study that will be chosen for full article review by means of the PRISMA flow diagram.³²

Data extraction

For articles meeting inclusion criteria, data will be extracted from included articles by two authors, as described in table 1. Missing data and raw data will be requested by e-mail from corresponding authors. Data will be extracted and managed using Excel. Data will only be extracted after acceptance of this protocol article.

Outcome measures

The primary outcome will be poor functional outcome (mRS 3–6) at follow-up after stroke or TIA. The secondary outcome will be recurrent stroke at follow-up at 90 days or follow-up periods used in each article. Primary and secondary outcomes will be summarised by OR or HR.

Risk of bias assessment

The risk of bias assessment will be performed qualitatively for each study. The Integrated Quality Criteria for Review of Multiple Study Designs tool will be used,³⁴ and data for the assessment will be collected as outlined in table 1. Risk of bias assessment will be jointly performed by two authors. Any lack of consensus will be adjudicated by consensus with the participation of the senior author. There is no planned assessment of meta-biases as the number of selected studies will likely be insufficient for meta-bias assessment.

Strategy for data synthesis

Heterogeneity assessment

Between-study heterogeneity will be quantified by I^2 statistic, with I^2 greater than 75% indicating considerable heterogeneity. In such a case, where $I^2 > 75\%$, results from each article will be reported descriptively rather than combined using meta-analysis.

Meta-analysis

Individual patient data will be synthesised from articles with available anonymised biochemical data and associated outcome measures (as described in table 1) if $I^2 \leq 75\%$. When available, the raw HOMA-IR scores from each article will be used to create quartiles that are consistent

across all included articles. Although follow-up intervals may vary between articles, the primary (mRS 3–6) and secondary (recurrent stroke) outcomes at follow-up will be treated dichotomously. The outcomes will be analysed using a random-effects meta-analysis based on the DerSimonian-Laird model,³⁵ and reported as risk ratios (highest three HOMA-IR quartiles compared with lowest HOMA-IR quartile) with accompanying 95% CI. Articles for which individual patient data are not available will be included if they use a quartile distribution of the HOMA-IR. Those articles that use a different HOMA-IR distribution will be included in the forest plot but will not be included in the summary measure of the meta-analysis.

Subgroup analysis

Patients with diabetes mellitus are more likely to suffer from non-cardioembolic strokes (atherothrombotic and lacunar) than cardioembolic strokes.^{36–38} As insulin resistance is a component and precursor of diabetes, it is possible that a similar association exists between insulin resistance and non-cardioembolic strokes. If sufficient data are available, a subgroup analysis of stroke aetiology will be performed (cardioembolic vs non-cardioembolic).

ETHICS AND DISSEMINATION

There were no animal or human samples or subjects used in this work. There are no ethical concerns to report. The results of the proposed systematic review and meta-analysis will be published in a peer-reviewed journal. The results will also be disseminated locally to the Ottawa Neurology Department, and will be presented at the American Academy of Neurology Conference and Canadian Neurological Sciences Federation Conference.

PATIENT AND PUBLIC INVOLVEMENT

Due to the nature of this article, a protocol for a systematic review was not necessary or appropriate to include patients or the public in the design of the research.

Contributors JH designed the project and wrote the manuscript. WK assisted in project design and manuscript writing. BD and DD provided guidance for project design. TR provided guidance for risk of bias methodology. AD is the librarian who

created the search strategy. MS provided supervision and guidance with project design. All authors assisted in manuscript editing and approved its contents.

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