Association of carotid intima–media thickness and dyslipidaemia in patients with type 2 diabetes: a protocol for systematic review and meta-analysis

Reneilwe Given Mashaba 1,2, Wendy Phoswa,1 Eric Maimela,1 Kabelo Mokgalaboni 1,2

INTRODUCTION

Diabetes mellitus (DM) is a complex chronic condition of carbohydrate metabolism characterised by the body’s inability to produce or respond to insulin.1,2 Patients with DM often present with comorbidities such as hypertension, dyslipidaemia, insulin resistance, obesity and hyperglycaemia, which increases their risk of cardiovascular diseases (CVDs)-related mortality.3–5 Moreover, a subclass of DM, type 2 DM (T2DM), is commonly known to have a high risk of secondary conditions such as anaemia due to reduced haematological indices.6,7 This may further increase the risk of CVDs in this group of patients.

Diabetes is characterised by a range of variables such as hyperglycaemia, insulin resistance and dyslipidaemia. These factors contribute to low-grade inflammation, an independent precursor and predictor of diabetes development. Consequently, individuals with T2DM are more susceptible to an accelerated progression of atherosclerosis.7,9 In addition to atherosclerosis, chronic inflammation has been reported to have a negative impact on the vascular system and

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The proposed study will comprehensively assess published evidence on carotid intima–media thickness and lipid profile in type 2 diabetes mellitus.
⇒ Different databases will be used to retrieve published studies.
⇒ The quality, risk of bias and evidence grading will be performed.
⇒ Subgroup analysis will be performed to find the exact source of heterogeneity.

ABSTRACT

Introduction Patients with diabetes mellitus (DM) often present with comorbidities such as hypertension, dyslipidaemia, insulin resistance, obesity and hyperglycaemia, which increases their risk of cardiovascular diseases (CVDs)-related mortality. Carotid intima–media thickness (CIMT), a biomarker for subclinical atherosclerosis, has been associated with overall CVD, especially in type 2 DM (T2DM). Hence, this protocol for systematic review and meta-analysis aims to review existing literature on the association of CIMT and dyslipidaemia in patients with T2DM.

Methods and analysis The proposed systematic review and meta-analysis will be conducted according to an updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols guideline. A comprehensive search of peer-reviewed studies on Google Scholar, PubMed, Science Direct and Web of Sciences databases will be conducted up to 30 June 2023. A meta-analysis of data extracted from selected studies will be performed to explore the association between dyslipidaemia and CIMT in patients with diabetes. The effect estimates will be reported as standardised mean differences/Cohen’s d and 95% CIs. A random effect model will be used in case of high heterogeneity whereas fixed-effect model will be used in the absence of heterogeneity. All statistical analysis will be performed using SPSS V.29.0 software. In cases of high heterogeneity, subgroup analysis will be performed based on study design, countries of publication and body mass index to identify potential sources of heterogeneity. Publication bias will be assessed graphically via funnel plots and statistically using Egger’s regression test. Sensitivity analysis will also be performed to evaluate the stability of the overall effect size and the grading of recommendations assessment, development and evaluation will be used to grade the quality of analysed evidence.

Ethics and dissemination As the proposed study will use secondary published data, approval will not be sought from the ethics committee. PROSPERO registration number CRD42023451731.
has been associated with intima calcification.\textsuperscript{10–12} Carotid intima–media thickness (CIMT) is regarded as an ideal biomarker for subclinical atherosclerosis and is associated with overall CVD, especially in patients with DM.\textsuperscript{13} 14 The CIMT is the distance from the lumen–intima interface to the media–adventitia interface of the artery wall, as measured on noninvasively acquired ultrasonography images of the carotid arteries.\textsuperscript{15} 16 It is associated with lipid accumulation and strongly predicts subclinical atherosclerosis.\textsuperscript{17} 18 CIMT is measured through a non-invasive higher, resolution ultrasonography test, which is able to detect the early stages of CIMT thickening.\textsuperscript{13} 15 It has been reported that a 0.1 mm increase in CIMT increases the relative risk of ischaemic heart disease by 15% and cerebral vascular disease by 18%.\textsuperscript{19} CIMT values are associated with hypercholesterolaemia regardless of genetic aetiology and predisposition.\textsuperscript{20} Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride are risk factors associated with the development of atherosclerosis.\textsuperscript{17} 21 T2DM has been reported to have a negative impact on the CIMT and the lipids profile. Moreover, CIMT has been associated with the development of CVDs. Given the increased risk of CIMT malfunctions and dyslipidaemia in T2DM, it is important to research the extent of risk patients with T2DM may have of developing future CVDs in order to best manage the condition. This study aims to review existing literature on the association of carotid intima thickness and dyslipidaemia in patients with diabetes.

METHODS AND ANALYSIS
Protocol and registration
This protocol for systematic literature review and meta-analysis is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols guideline 2015\textsuperscript{22} (online supplemental appendix 1). The protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023451731.

Ethics approval
The present study will use data pooled from studies published in peer-reviewed journals and will, therefore, not require ethical approval from an institutional ethics committee.

Patient and public involvement
None.

Objectives and outcomes questions
The objective of this is to evaluate the association of carotid intima thickness and dyslipidaemia in patients with diabetes. The study aims to answer the research questions based on Population, Exposure, Compares, Outcomes and Study design criteria:

What is the association between CIMT and risk of developing dyslipidaemia in patients with diabetes?

PICO eligibility criteria
\begin{itemize}
  \item Population: Type 2 diabetic adults aged 18 years and above.
  \item Exposure: T2DM.
  \item Comparator: The review will include studies that have patients with non-diabetes to serve controls and aged 18 years and above.
  \item Outcomes: Dyslipidaemia and impaired CIMT.
  \item Study design: The proposed systematic review and meta-analysis will include cross-sectional studies, prospective case controls, prospective and retrospective cohorts.
\end{itemize}

Study selection
The studies for inclusion will be selected based on eligibility criteria and this will be performed by two (KM and RGGM) investigators independently to minimise the risk of selection bias. The initial screening process will include screening by title, abstracts, keywords and the overall aim of the study guided by PECO guidelines and the eligibility criteria. Studies deemed appropriate for the review and meta-analysis based on screening the title and abstract will be downloaded by the investigators independently for the full-text screening process. In case of disagreements regarding screening, data extraction and quality assessment, a final decision will be made by contacting independent investigators (WP and EM) to evaluate the study domain in question.

Inclusion criteria
1. Studies investigating the association of CIMT and dyslipidaemia in type 2 patients with diabetes.
2. Used the ultrasound method to measure CIMT.
3. Measured lipids profile (total cholesterol, triglycerides, low high-density lipoprotein, low-density lipoprotein).
4. Included participants diagnosed with T2DM and non-diabetic controls.
5. Published in English. In cases where a study reported CIMT and lipids profiles in T2DM for different DM duration periods, the longest period will be considered.

Exclusion criteria
1. Studies without measurement of CIMT or lipid profiles.
2. Studies in patients with other conditions other than T2DM.
4. Systematic reviews and meta-analysis or any reviews.

Search strategy
Google Scholar, PubMed, Science Direct and Web of Sciences databases will be searched up to 30 June 2023, following a standardised strategy developed following standardised medical subject headings (MeSH) terms and search strategy. Reference lists of the retrieved studies will also be searched to identify additional eligible studies.
The following medical subject heading (MeSH) will be used to identify relevant studies from databases: “carotid intima-media thickness” ([MeSH] OR “CIMT” [MeSH] OR “carotid atherosclerosis” [MeSH]) AND “dyslipidemia” ([MeSH] OR “high total cholesterol”, “high triglycerides”, “low high-density lipoprotein cholesterol”, and “elevated low-density lipoprotein cholesterol”) AND “type 2 diabetes mellitus” ([MeSH] OR “hyperglycemia”). A piloted search strategy is attached in supplementary file (refer to online supplemental appendix B).

**Data management**

**Data extraction and quality assessment**

The investigators (RGM and KM) will independently extract the following data from eligible studies: name of the first author, year of publication, country, sample size, age, T2DM status, the mean and SD for total cholesterol, low-density lipoprotein, high-density lipoprotein and CIMT in to excel spreadsheet. The main findings of the studies will be summarised. The general characteristics of all analysed studies will be presented in tabular form to show the basics characteristics of included studies. Zotero 6.0.20 reference manager will be used to compile identified studies into a single folder in which the process of duplicate removal will be performed. Quality will be assessed by RGM and KM following guidelines from the Newcastle-Ottawa Scale. This method considers three main domains: selection, comparability and outcome across different study designs. Any disagreement will be resolved by inviting an independent investigator (WP and EM).

**Statistical analysis**

Meta-analysis will be performed in case where two or more studies are available reporting on same outcome measures, otherwise narrative approach will be taken. Data extracted from each study will be analysed using IBM SPSS statistical software (V.29) and metaHun, online meta-analysis software. Sample size, mean and corresponding SD will be used to estimate the effect size across all outcomes (CIMT, lipid profiles) in T2DM compared with controls. In cases where the selected reported data in the form of median and ranges, this will be converted to mean and SD following guidelines by Wan et al.\(^\text{19}\) The effect size will be reported as Cohen’s d/standardised mean difference and 95% CIs. Forest and funnels plots will be used to present the overall effect estimates. The magnitude of effect size will be categorised as small, medium and large when equivalent to 0.2, 0.5 and 0.8, respectively. Probability values of <5% will be regarded as statistically significant. The p<0.05 for Egger’s test will be classified as potential publication bias.

**Subgroup analysis**

The heterogeneity in quantitative analysis is defined as variations in study outcomes between studies. We will use the I\(^2\) statistic test to assess statistical heterogeneity.\(^\text{20}\) The I\(^2\) values of 50% and >75% will be classified as minimal and substantial statistical heterogeneity, respectively. In the presence of heterogeneity, random-effect model meta-analysis will be used across the studies. However, in cases of no evidence of heterogeneity (I\(^2\) =0%), a fixed-effect model meta-analysis will be conducted. Should there be evidence of heterogeneity (I\(^2\) >50%), subgroup analysis will be performed based on predetermined covariates of interest such as age, gender, population size and country where the study was performed.

**Sensitivity analysis**

Sensitivity analysis will be explored by one study exclusion method to confirm the stability of the effect size.\(^\text{24}\) Any changes observed in the reanalysed effect size will be compared with the original effect size to identify the magnitude of the change.

**Publication bias**

Publication bias plays a role in research, in this proposed study publication bias will be assessed if there are more than ten studies analysing the same parameters. Therefore, in this study, we will assess publication graphically by visualising funnel plots and statistically with the Egger’s regression test.\(^\text{25}\) Any asymmetry noted through funnel plots will imply the presence of bias while a symmetrically shaped funnel plot will indicate the absence of publication bias. Additionally, Egger’s test p≤0.05 will confirm the presence of publication bias while p>0.05 will exclude publication bias among the studies analysed.

**Grading of evidence**

The grading of recommendations assessment, development and evaluation will be used to grade the quality of analysed evidence using GRADEPro.\(^\text{26}\) All domains including risk of bias, inconsistency, indirectness, imprecision and publication bias will be evaluated independently by RGM and KM. Quality will be judged as low, very low, moderate of high based on the upgrading or down-grading of each domain.

**DISCUSSION**

T2DM predisposed individuals to an elevated risk of developing CVD compared with non-diabetics. The proposed systematic review and meta-analysis will highlight the association of CIMT and dyslipidaemia in patients with diabetes. The findings of this review and meta-analysis will add to the body of knowledge on T2DM treatment. It will also inform and contribute new ways of treating T2DM and highlight the importance of considering components such as lipids profiles and CIMT to promote a holistic approach to T2DM treatment. In addition, armed with the results from the review and meta-analysis, patients with diabetes may take into consideration the CIMT and lipids profiles to make better health decisions.
Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

N/A

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Not applicable

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCIDs

Reneilwe Given Mashaba http://orcid.org/0000-0001-6235-2325
Kabelo Mokgalaboni http://orcid.org/0000-0002-3224-7433

REFERENCES