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Examining endothelial function and carotid artery disease in patients with inflammatory bowel disease: a systematic review protocol

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ABSTRACT

Introduction Patients with inflammatory bowel disease (IBD) might be at an increased risk for the development of cardiovascular disease (CVD). The present protocol is developed to review and analyse published data to determine if patients with IBD have an increased CVD burden.

Methods and analysis We will conduct a systematic review of all observational studies that examine endothelial function, arterial stiffness and carotid intima-media thickness in patients with IBD. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and study quality will be assessed using the Newcastle-Ottawa Scale. If sufficient data are available, a meta-analysis will be conducted. The overall effect sizes will be estimated using both fixed effects models and random effects models. Statistical heterogeneity will be calculated using Higgin's (I^2) tests. Subgroup analyses, conditional number of studies retrieved and their sample size, will be stratified according to participant disease category or gender or disease activity.

Ethics and dissemination Formal ethics approval is not required as individual data will not be collected. The results will be disseminated through peer-reviewed publications, conference presentations and scientific news releases.

PROSPERO registration number CRD42021274093.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study employs a broad search strategy from multiple large databases, including PubMed, EMBASE, Cochrane library and Web of Science.
⇒ The data reporting will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
⇒ The study may be impacted by significant heterogeneity in the included studies due to differences in diagnostic tests, disease activities and the presence of traditional cardiovascular risk factors.

INTRODUCTION

Rationale

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality despite aggressive treatment of traditional risk factors.[1] Systemic inflammation and endothelial cell dysfunction are considered among the key factors that are critically involved in the development and progression of CVD.[2 3] Indeed, patients with chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and psoriasis have an increased risk of arterial and venous thromboembolic events.[4] During the past decade, several studies have suggested that patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), might be at an increased risk for CVDs including coronary artery disease and arterial and venous thromboembolic events.[5–9]

Endothelial dysfunction is critically involved in the development and progression of atherosclerosis and related vascular diseases. Non-invasive vascular function tests such as flow-mediated dilatation (FMD), nitroglycerin-mediated dilatation (NMD) and reactive hyperemia assessed by peripheral arterial tonometry (RH-PAT) have been used to evaluate endothelial function in vivo.[10] The assessment of endothelial function via brachial artery FMD has been widely used in human subjects. One of the principal mediators for FMD is endothelium-derived nitric oxide (NO).[11] NMD, an index of endothelium-independent vasodilation, assessed by sublingual administration of nitroglycerine, has been used to determine if impairment in vasodilation is due to a loss in smooth-muscle cell integrity or the inability of endothelial cells to release NO.[12] RH-PAT does not directly measure vasodilation, rather it measures augmentation in finger pulse pressure, which is believed to reflect microvascular dilation through both endothelium-dependent and endothelium-independent mechanisms.[13]

Arterial stiffness is a growing epidemic associated with increased risk of CVDs and assessed primarily using pulse wave velocity (PWV) and augmentation index (AIx). Increased arterial stiffness is a well-established indicator for vascular endothelial dysfunction and an independent predictor of cardiovascular events.[14] AIx has also been shown to be associated with increased cardiovascular risk.[15] One of the important features for arterial atherosclerosis is smooth muscle hyperplasia with increased carotid intima-media thickness (cIMT), a strong predictor of future vascular events including myocardial infarction and stroke.[16] Although there are numerous studies evaluating endothelial function, arterial stiffness and cIMT in patients with IBD,[17 18] there is no comprehensive study to systematically review and summarise the data from these individual studies.

Objective

The objective of this review is to systematically evaluate endothelial function, arterial stiffness and cIMT in patients with IBD.

METHODS

Patients and public involvement

No patient was involved.

Study selection

Observational studies (case-controlled, cross-sectional or cohort) will be included if meeting the following criteria:[1] investigating endothelial function and arterial stiffness or their surrogate markers in patients with IBD (including patients with UC or CD) and controls;[2] reporting measurements of cIMT in patients with IBD and control subjects;[3] and written in English. Every effort will be made to include all the studies that meet these criteria.

Search strategies

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[19] has been prospectively registered with PROSPERO. A comprehensive literature search and review will be conducted through the electronic databases for published studies at PubMed (1945 to present), EMBASE (1974 to present), Cochrane library (1996 to present) and Web of Science (1900 to present). We will use the Medical Subject Heading terms and keywords in all possible combinations using Boolean operators with the following search strategies: 'Inflammatory Bowel Diseases', 'Inflammatory Bowel Disease', 'Bowel Diseases, Inflammatory', 'IBD', 'Ulcerative Colitis', 'Colitis, Ulcerative', 'Idiopathic Proctocolitis', 'Colitis Gravis', 'Inflammatory Bowel Disease, Ulcerative Colitis Type', 'UC', 'Crohn Disease', 'Crohn's Disease', 'Crohn's Enteritis', 'CD', 'endothelium-dependent flow-mediated dilatation', 'endothelium-independent flow mediated dilatation', 'FMD', 'nitroglycerin-mediated dilatation', 'NMD', 'endothelial function', 'peripheral arterial tonometry', 'PAT', 'reactive hyperemia', 'vascular stiffness', 'arterial stiffness', 'pulse wave velocity', 'PWV', 'augmentation index', 'AIx', 'intima-media thickness' and 'IMT' (see online supplemental appendix 1). The references of all full-text articles will be thoroughly reviewed to identify other potentially relevant articles. All articles will be initially screened and evaluated according to their titles and abstracts. Articles describing animal studies only and non-English language articles will be excluded. Subsequently, the full articles will be evaluated by two independent reviewers (HW and TH) for eligibility. Articles will be downloaded into Endnote and any duplicates will be deleted. Data collection is anticipated to start in February of 2022 and to be completed by October 2022.

Data extraction

Two independent investigators (HH and MX) will screen each article and extract the data. In case of disagreement, a third investigator will be consulted (MAH). Discrepancies will be resolved by consensus. Information will be collected on study design, country of origin of the studies, sample size, major clinical and demographic variables, techniques for assessing endothelial function and arterial stiffness and IMT, as well as study outcomes associated with FMD, NMD, RH-PAT, PWV, AIx and cIMT.

Quality assessment

Based on the characteristics of the included studies, the methodological quality of each study will be evaluated and scored by two independent investigators (CX and ZL) using the Newcastle-Ottawa Scale,[20] which is specifically developed to assess the quality of non-randomised observational studies. The scoring system consists of three major components: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. The total scores for each study range between 0 and 9, a higher score representing better methodological quality.

Outcomes

The outcomes of the review will be grouped into the following headings.

Endothelial function: will include direct measurements of FMD, NMD or RH-PAT.

Arterial stiffness: will be assessed by central PWV, peripheral PWV, brachial-ankle PWV and AIx.

Intima-media thickness: will primarily include carotid IMT. If available, aortic or femoral arterial IMT will also be included.

ANALYSIS

Descriptive analysis

A narrative synthesis of the outcomes of the selected studies will be presented in the final review. This will include the following:

1. Type of study design, control group and sample size.

2. Major clinical and demographic variables: disease activity (active or inactive), disease extent and illness behaviour (Montreal classification),[21] if possible.
3. Techniques for assessing endothelial function, arterial stiffness and IMT.
4. Study outcomes: this will include the change in FMD, NMD, RH-PAT, PWV, AIx and cIMT.

Statistical analysis

Meta-analysis (where possible) will be conducted to assess endothelial function, arterial stiffness and cIMT in patients with IBD. Difference between patients and controls will be calculated using the standardised mean difference (SMD) for continuous variables. These estimates and their 95% CI will be illustrated using a forest plot. The overall effect sizes will be estimated using both fixed effects models and random effects models. Statistical heterogeneity will be calculated using Higgin's (I^2) tests. Subgroup analyses, conditional on the number of studies and their sample sizes, will be stratified based on disease category (eg, UC/CD) or sex (male/female) or disease activity (eg, active/inactive).

Potential publication and small sample size bias will be assessed by visual inspections of funnel plots and Egger's Test. To explore the effect of main factors of interest on predicting SMD, meta-regression analysis will be conducted with restricted maximum likelihood estimation method, controlling for potential confounders including disease activity, treatment and coexistence of traditional cardiovascular risk factors. All statistical analyses will be conducted using R package metafor.[22] A p value<0.05 will be considered statistically significant for all analyses.

Contributors HW, ZL and HH conceived the idea and planned and designed the study protocol. HW wrote the first draft. TH, HH and MX planned the data extraction and statistical analysis. CX and ZL provided critical insights. MAH and ZL critically reviewed and modified the manuscript. All authors have reviewed and approved the manuscript.

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