International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Unveiling TIMPs: A Systematic Review of Their Role as Biomarkers in Atherosclerosis and Coronary Artery Disease

INPLASY202470070
doi: 10.37766/inplasy2024.7.0070
Received: 19 July 2024
Published: 19 July 2024

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ADMINISTRATIVE INFORMATION

Support - FRGS 2021-1.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202470070

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 July 2024 and was last updated on 19 July 2024.

INTRODUCTION

Review question / Objective The study aims to determine the specific role that tissue inhibitors of metalloproteinase (TIMPs) play in the complex landscape of atherosclerosis. This review will consolidate current evidence and discuss the implications of TIMPs as emerging biomarkers in atherosclerosis, fostering a comprehensive understanding of their diagnostic and prognostic potential in cardiovascular health. Population (P): Patients with and without coronary artery disease (CAD), Intervention (I): None, Comparison (C): Non-CAD patients or healthy, Outcome (O): The measurement of TIMPs level, and Study (S): Human stud.

Rationale 1) Atherosclerosis was the main physiology hallmark for CAD, a leading cause of mortality and morbidity worldwide. 2) TIMPs, an inhibitory endogenous protein for MMPs have emerged as potential candidates for monitoring atherosclerotic development. 3) However, there is an imbalance in research which focuses mainly on MMPs' actions and often overlooks the important role of TIMPs. 4) Recognizing and validating novel biomarkers, particularly those involving TIMPs, present a promising avenue for enhancing risk stratification, early diagnosis, and monitoring the effectiveness of therapeutic interventions.

Condition being studied Studies that measure TIMPs levels among CAD patients, non-CAD, and healthy individuals. Both gender (male and female) regardless of ethnicity were also included.

METHODS

Search strategy The literature search was carried out across four internet databases (Pubmed, Scopus, Web of Science, and Ovid), with inclusion criteria limited to studies published between 2014 and January 2024. The keywords used for the search were (TIMP OR “Tissue inhibitor of metalloproteinases”) AND (Atherosclerosis OR “Ischemic heart disease” OR “Cardiovascular disease” OR “Coronary artery disease” OR “Acute coronary syndrome” OR “Myocardial infarction).

Participant or population Patients diagnosed with coronary artery disease (CAD) which includes patients with myocardial infarction (MI), acute coronary syndrome (STEMI, NSTEMI, unstable angina), stable coronary heart disease (CHD), and coronary atherosclerosis. Normal healthy people also will be included.

Intervention Not applicable.

Comparator TIMPs levels were measured in a group of patients diagnosed with CAD compared to control healthy individuals.

Study designs to be included Human study (case-control, cross sectional, and cohort).

Eligibility criteria Inclusion criteria encompassed (1) full-text of peer-reviewed original articles written in English, (2) research examining TIMP and its association with atherosclerosis, and (3) clinical studies involving adult patients diagnosed with CAD confirmed via coronary angiogram, regardless of gender. The exclusion criteria comprised: (1) original articles not in English, (2) reviews, conference abstracts, editorials, newsletters, books, and book chapters, (3) in vitro research, and (4) studies involving animals.

Information sources The articles were searched from online databases through Universiti Kebangsaan Malaysia (UKM) Library Website. Then, the articles were exported and downloaded to the Mendeley.

Main outcome(s) A total of 6141 were identified and only nine studies were included. Among the nine studies, six reported a positive association between higher levels of TIMPs and an increased risk of atherosclerosis. Conversely, three studies support low TIMPs with high CAD risk. This divergence in findings underscores the complexity of the relationship between TIMPs and atherosclerosis. In addition, meta-analysis from two suitable studies showed that the HR (95% CI) was 1.42 (1.16–1.74; $p<0.001$; $I2=0\%$) and found TIMP-1 was correlated well with major adverse cardiovascular events (MACE). In conclusion, the existing evidence supports the notion that TIMPs can serve as biomarkers for predicting atherosclerosis among CAD patients. However, further exploration is warranted through larger-scale human studies, coupled with in vitro and in vivo investigations.

Additional outcome(s) No additional outcome.

Quality assessment / Risk of bias analysis Three reviewers (UV, NS, and AAH) conducted independent assessments of the selected articles' risk of bias. The Newcastle-Ottawa Scale (NOS) was utilized to critically evaluate the quality of risk of bias for each of the articles. In cohort and cross-sectional studies, the NOS evaluated the selection of study groups (exposed and non-exposed), their comparability, and the assessment of outcomes. While, for case–control studies, the NOS assessed the selection of study groups (cases and controls), their comparability, and the determination of exposure for both cases and controls. Total of eight items from the three domains could receive a star rating, with each item being could be awarded a minimum of one star or a maximum of two stars. Studies receiving total score of seven to nine stars were considered high-quality, those with four to six stars were considered fair quality, and those with one to three stars were considered low-quality.

Strategy of data synthesis The article selection process involved three phases. Initially, articles were screened based on their titles and types, with review or editorial articles being disregarded. Subsequently, abstracts were scrutinized to eliminate irrelevant articles concerning TIMPs and atherosclerosis. Finally, the remaining articles underwent thorough full-text analysis, and those not meeting the inclusion criteria were excluded. For data extraction, three researcher (AA, UV and NS) independently compiled information such as the study's first author, design, subject characteristics including age and gender, methods of TIMP measurement, and the association between TIMPs and atherosclerosis into a table.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction English.

Country(ies) involved Malaysia.

Keywords Tissue inhibitor of metalloproteinases; atherosclerosis; Ischemic heart disease; cardiovascular disease; coronary artery disease; acute coronary syndrome; myocardial infarction.

Contributions of each author

Author 1 - Amilia Aminuddin - Formulated the research question, objectives, inclusion and exclusion criteria; conducted data collection, extraction, writing, and final proofreading of the manuscript.
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