

Role of Interleukins in the Pathogenesis of Coronary Heart Disease: A Literature Review

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Dear Editor

The reviewers raised the following queries which are explained below.

A point-by-point response to the reviewers' reports

We would like to express our gratitude to the reviewers for dedicating their time to thoroughly evaluate the manuscript and providing us with insightful and constructive feedback.

Reviewer #1:

The manuscript offers a comprehensive review of the roles of interleukins (ILs) in the pathogenesis of coronary heart disease (CHD), a topic of increasing significance as our understanding of inflammatory pathways in cardiovascular diseases continues to grow. However, there are several areas that require enhancement to elevate the quality and impact of this review.

1. the manuscript predominantly summarizes existing literature without delving into a critical evaluation. A more in-depth exploration of controversies, gaps in research, and limitations of current studies is essential. For instance, the dual role of IL-10 as both a pro-inflammatory and anti-inflammatory cytokine is a complex issue that warrants a more critical discussion. The author should consider including a dedicated section that synthesizes the collective roles of ILs in CHD, integrating findings across different ILs to provide a holistic and cohesive view of their involvement in the disease process.

Author's response: Thank you for your feedback. We have added the new information regarding the exploration of controversies, research gaps, limitations of current studies, dual role of interleukin 10 and gave the information about as collective roles of interleukins in CHD in the revised manuscript which is yellow highlighted.

'The dual role of IL-10 as both a pro-inflammatory and anti-inflammatory cytokine stems from its context-dependent effects and the diverse cellular pathways it influences. The cytokine classification as pro- or anti-inflammatory may not apply to IL-10's pleiotropic activities. Numerous data indicate that IL-10 improves natural killer cell activity, which increases antigen availability by destroying pathogens. Moreover, IL-10 prevents antigen-presenting cells (APCs) from maturing, which maintains their capacity to absorb antigens while also impeding their migration to draining lymph nodes.'

'The development of coronary heart disease and atherosclerosis is significantly influenced by inflammation. Interleukins, a subset of cytokines, play a critical role in the pathogenesis of

CHD by mediating inflammation, which is a key factor in atherosclerosis and its complications. Interleukins such as IL-1 β and IL-6 are released in response to endothelial injury caused by risk factors like hypertension, dyslipidemia, smoking, and hyperglycemia. These cytokines promote the expression of adhesion molecules on endothelial cells, facilitating the recruitment of monocytes and T-cells to the arterial wall. Once monocytes migrate into the intima, they differentiate into macrophages, ingest oxidized low-density lipoprotein, and form foam cells.

IL-1 β and IL-8 amplify this inflammatory cascade by recruiting more immune cells and sustaining the inflammatory environment. Chronic inflammation driven by interleukins leads to the accumulation of foam cells, smooth muscle cell proliferation, and extracellular matrix deposition, contributing to plaque formation. IL-1 β , and IL-6, are involved in destabilizing atherosclerotic plaques by inducing matrix metalloproteinases, which degrade the fibrous cap of plaques. A thin fibrous cap increases the risk of plaque rupture, leading to thrombosis. Elevated levels of IL-6 are associated with increased fibrinogen production, which enhances blood clot formation following plaque rupture.

During acute coronary events, pro-inflammatory interleukins, including IL-1 β and IL-6 surge in the circulation. These cytokines amplify the systemic inflammatory response, exacerbate endothelial dysfunction, and promote further thrombosis. IL-1 β and IL-6 exacerbate myocardial injury by sustaining inflammation and oxidative stress in the coronary vessels. Inflammatory markers such as CRP, IL-6, and IL-1 β are useful in CHD risk prediction and monitoring. Statin therapy can lower the risk of CHD in individuals with increased CRP but without hyperlipidemia. To find more new serum indicators with greater specificity for coronary artery plaque inflammation, extensive research is now underway. Future cardiovascular incidents may be avoided by using certain inhibitors of vascular inflammation in addition to statins, which are drugs that reduce low-density lipoprotein cholesterol. ‘

2. the narrative structure of the manuscript often feels fragmented. Each IL is discussed in isolation, without adequately integrating their interrelationships or their combined impact on the pathogenesis of CHD. This approach can make it difficult for readers to grasp the bigger picture. Including a concluding synthesis at the end of each section would greatly aid in consolidating the information and highlighting the interconnectedness of the various ILs in the context of CHD.

Author’s response: We have added new information regarding this point in the revised manuscript which is yellow highlighted.

3. the methodology for selecting articles is not sufficiently detailed. The inclusion and exclusion criteria for the studies reviewed are notably absent. This lack of clarity affects the reproducibility and reliability of the review, which are crucial aspects of any scientific work. A more transparent and detailed description of the selection process would strengthen the credibility of the findings presented.

Author's response: We have added the inclusion and exclusion criteria in the methodology section in the revised manuscript which is yellow highlighted.

‘According to the literature, there are various interleukins, however, this review article summarizes the role of interleukins such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, and IL-10 in the pathogenesis of CHD. The literature was searched until January 17, 2025, using several databases such as Google Scholar, PubMed, and Science Direct. Keywords such as “Coronary heart disease” “Interleukins,” “Inflammation,” and “pathogenesis,” were used. Only English-language clinical research was taken into account. While preference was given to papers published recently, there was no strict timeframe for publication dates. The inclusion criteria encompass peer-reviewed studies (clinical trials, cohort studies, case-control studies, systematic reviews, meta-analyses, or experimental studies) examining interleukins in CHD. Conversely, the excluded criteria pertain to studies that specifically address different cardiovascular diseases.’

4. the manuscript contains repetitive content, such as the roles of ILs in inflammation and atherosclerosis. While repetition can sometimes be useful for emphasis, in this case, it detracts from the conciseness of the review. Consolidating repetitive points into a more streamlined narrative would enhance the clarity and efficiency of the communication.

Author's response: We have removed the repetitive content and tried to give clear information according to our aim of this article and it is described in the revised manuscript which is yellow highlighted.

5. the manuscript has several grammatical errors and awkward phrasings that significantly impact readability. Examples include incomplete sentences and the misuse of tenses, such as the phrase "It was discovered that a suitable lifestyle modification might reduce IL-1Ra levels." A thorough language review is necessary to correct these grammatical errors and improve the overall readability of the manuscript. This would involve not only fixing the identified issues but also ensuring that the language flows smoothly and is easily comprehensible to the target audience.

Author's response: We have revised the whole manuscript removed the awkward phrasings and improved the grammatical errors and it is described in the revised manuscript which is yellow highlighted.

‘It was discovered that an appropriate lifestyle change reduced IL-1Ra levels and lessened the increased risk of CHD it presented.’

6. the manuscript would benefit from more detailed figure legends and explicit references to figures within the text. Additionally, the inclusion of a summary table that highlights the roles, mechanisms, and therapeutic implications of each IL would be a valuable addition. This would provide readers with a quick reference point and help to consolidate the key information presented in the review.

Author’s response: We have made new tables which give information about interleukins and their therapeutic implications in the revised manuscript with yellow highlighted.

7. Include a dedicated section on future research directions, emphasizing gaps in knowledge, potential biomarkers, and therapeutic targets among the ILs.

Author’s response: We have this information in new headings which is described in detail in the revised manuscript.

Reviewer #2:

1. The methods section is vague and does not provide sufficient detail on how the literature was selected and analyzed. Statements like "preference was given to papers published recently" are not substantiated by a robust inclusion/exclusion criteria or systematic review methodology.

Author’s response: Thank you for the positive feedback. It is a literature review article, we have improved the methodology by adding information about inclusion and exclusion criteria.

‘According to the literature, there are various interleukins, however, this review article summarizes the role of interleukins such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, and IL-10 in the pathogenesis of CHD. The literature was searched until January 17, 2025, using several databases such as Google Scholar, PubMed, and Science Direct. Keywords such as “Coronary heart disease” “Interleukins,” “Inflammation,” and “pathogenesis,” were used. Only English-language clinical research was taken into account. While preference was given to papers published recently, there was no strict timeframe for publication dates. The inclusion criteria encompass peer-reviewed studies (clinical trials, cohort studies, case-control studies, systematic reviews, meta-analyses, or experimental studies) examining interleukins in CHD. Conversely, the excluded criteria pertain to studies that specifically address different cardiovascular diseases.’

2. Many sections merely regurgitate findings from cited studies without critically evaluating their strengths, weaknesses, or implications. For instance, the discussion on IL-6's role in CHD does not contextualize its predictive value or limitations in clinical settings.

Author's response: We have revised the point in the revised manuscript.

'IL-6 is not specific to CHD and can be elevated in various inflammatory conditions, infections, and autoimmune diseases, limiting its utility as a stand-alone diagnostic marker. IL-6 levels may fluctuate depending on acute and chronic inflammation, complicating its reliability as a consistent biomarker. There is no universally accepted cutoff for IL-6 levels in predicting CHD, making it challenging to integrate into clinical practice. IL-6 adds predictive information, but when used alongside established markers like high-sensitivity CRP and lipid profiles, its incremental value may be modest. While IL-6 has potential as a biomarker for cardiovascular risk stratification, its role is better suited as part of a multimarker approach rather than as a solitary measure. Further research is required to establish standardized guidelines for its use in clinical practice and to better delineate its utility in different patient populations, such as those with metabolic syndrome or chronic inflammatory diseases.'

3. Figures 1 and 2 are inadequately described in the text. Their content, relevance, and design appear generic, offering little to support the manuscript's claims.

Author's response: We have revised this point in the revised manuscript.

Incomplete Discussion on Therapeutic Strategies: 4. The manuscript contains numerous grammatical errors and awkward phrasing, such as "This review article discusses only major interleukins which were not reported collectively in coronary heart disease." These issues detract from readability and professionalism.

Author's response: We have a new section about therapeutic strategies in the revised manuscript and removed the grammatical errors and awkward phrasing.

'Many studies have reported cytokines cause the pathogenesis of CHD. The review aims to report the role of interleukins such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, and IL-10 in the pathogenesis of CHD, therapeutic strategies, identify knowledge gaps and highlight future research directions to improve the understanding and management of CHD.'

Redundancy: 5. Several sections, particularly in the introduction and the discussion of individual interleukins, repeat similar points, leading to unnecessary verbosity.

Author's response: We have revised points in the revised manuscript with yellow highlighted.

6. While the manuscript cites many studies, the citations are not always integrated thoughtfully into the text. Furthermore, the reliance on older studies in some cases (e.g., references from the 1990s) undermines the relevance of the conclusions.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

7. Some terms are used inconsistently. For example, "atherosclerosis" and "CHD" are often conflated without explanation, which could confuse readers.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

8. Reorganize the manuscript around a central theme, such as the interplay between specific interleukins and inflammation in CHD. Provide a more cohesive narrative.

Author's response: We have revised the central theme and added the new information about the interplay between specific interleukins and inflammation in CHD in the revised manuscript with yellow highlighted.

Critical Analysis: 10. Adopt a systematic approach to the literature review. Define clear criteria for study selection and provide a flowchart summarizing the search and screening process. Expand the discussion on therapeutic strategies, focusing on their clinical relevance, current limitations, and future directions. Redesign figures to make them more informative and visually engaging. Clearly explain their content and relevance in the text. Proofread the manuscript for grammar, syntax, and clarity. Avoid redundancy and streamline the content for better readability. Incorporate more recent studies to enhance the manuscript's relevance and credibility.

Author's response: We have revised these points in the revised manuscript with yellow highlighted.

Reviewer #3:

Comments to authors The manuscript comprehensively reviews the role of interleukins (ILs) in the pathogenesis of coronary heart disease (CHD). While it addresses critical aspects of the topic, several areas require attention to enhance its scientific rigor, clarity, and overall quality. It systematically summarizes the current knowledge on interleukins in CHD but would benefit from a more in-depth analysis of novel research findings.

Following are a few suggestions for further improvements:

Abstract The abstract effectively summarizes the manuscript's main points, including the critical role of interleukins in CHD. It highlights the focus on inflammation and potential therapeutic strategies targeting ILs. However, the uniqueness of the methodology could be emphasized further to underscore the novelty of the research.

Author's response: We have revised these points in the revised manuscript with yellow highlighted.

Introduction The introduction provides an adequate background on the role of ILs in inflammation and CHD. However, it should explicitly highlight the current gaps in understanding or unresolved questions in the field. For instance, specific unknowns about the mechanisms by which certain ILs influence CHD progression or the limitations of existing studies could be elaborated. Additionally, the study's objectives should be clearly stated to guide the reader.

Author's response: We have revised these points in the revised manuscript with yellow highlighted.

Materials and Methods/Experimental Procedure The manuscript lacks a dedicated methods section. As a review, it would benefit from a brief explanation of how literature was selected, including the inclusion/exclusion criteria, databases searched, and keywords used. This would provide transparency and allow readers to assess the comprehensiveness of the review. If the review synthesizes experimental data, details about the methods employed in those experiments should be included.

Author's response: We have revised these points in the revised manuscript with yellow highlighted.

'According to the literature, there are various interleukins, however, this review article summarizes the role of interleukins such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, and IL-10 in the pathogenesis of CHD. The literature was searched until January 17, 2025, using several databases such as Google Scholar, PubMed, and Science Direct. Keywords such as "Coronary heart disease" "Interleukins," "Inflammation," and "pathogenesis," were used. Only English-language clinical research was taken into account. While preference was given to papers published recently, there was no strict timeframe for publication dates. The inclusion criteria encompass peer-reviewed studies (clinical trials, cohort studies, case-control studies, systematic reviews, meta-analyses, or experimental studies) examining interleukins in CHD. Conversely, the excluded criteria pertain to studies that specifically address different cardiovascular diseases.'

Results The results are presented clearly and understandably. However, there is no detailed explanation of how the findings directly relate to the methods described. The use of statistical

analysis is mentioned, but the specifics of the data interpretation and its consistency with the study's methods need to be elaborated.

Author's response: We have revised these points in the revised manuscript with yellow highlighted. We had reported the statistical analysis of other studies but we did not apply any statistical analysis. It is a literature review, not a meta-analysis.

Discussion The study's limitations are not discussed, which would have provided a more balanced view. It would also be beneficial to propose future research directions to address the unanswered questions.

Author's response: We have revised these points in the revised manuscript with yellow highlighted.

Language The manuscript is well-written, with minimal grammatical and spelling errors. The language is clear and concise, though it could benefit from minor improvements in sentence structure to enhance readability.

Author's response: We have revised the manuscript and removed the grammatical errors and awkward phrasing.