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Impact of Rheumatoid Arthritis on Endothelial Function: A Comprehensive Meta-Analysis of Vascular Biomarkers and Therapeutic Interventions

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that not only affects the joints but also increases the risk of cardiovascular disease due to endothelial dysfunction. This systematic review and meta-analysis aim to evaluate the extent of endothelial dysfunction in RA, its association with biomarkers such as nitric oxide (NO), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), and the impact of anti-inflammatory therapies on endothelial function. A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science, and studies meeting specific inclusion criteria were included for analysis. The pooled results showed significant impairment in endothelial function in RA patients, with lower reactive hyperemia index (RHI) and laser Doppler vasoreactivity compared to healthy controls. Subgroup analysis revealed that longer disease duration was associated with greater microvascular impairment and less therapeutic reversal. Anti-inflammatory therapies, particularly anti-TNF-α agents, demonstrated improvements in endothelial function, though the effects were more modest in patients with prolonged disease. No significant publication bias was detected. This study highlights the importance of early intervention in RA to reduce endothelial dysfunction and cardiovascular risk, emphasizing the potential for therapies targeting endothelial health in RA patients. Further research is needed to explore long-term treatment effects and novel therapies for improving vascular health in RA.

Keywords: *Rheumatoid arthritis, endothelial dysfunction, nitric oxide, ICAM-1, VCAM-1, cardiovascular risk, biomarkers, systematic review, meta-analysis*

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that primarily affects the joints but is also associated with an increased risk of cardiovascular disease (CVD) (Jia et al., 2024). One of the key factors contributing to this heightened cardiovascular risk is endothelial dysfunction, which plays a critical role in the development of atherosclerosis and other cardiovascular complications (Drożdż et al., 2023). Endothelial dysfunction is characterized by impaired vascular reactivity, a decrease in nitric oxide (NO) bioavailability, and an increase in circulating adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Aleksandrowicz et al., 2025). These alterations in vascular function are thought to be driven by the chronic systemic inflammation observed in RA (Wang and He, 2024).

Despite the growing recognition of endothelial dysfunction as a major contributor to cardiovascular morbidity in RA, its exact pathophysiological mechanisms and the impact of disease duration and treatment remain unclear (Ambrosino et al., 2022). Previous studies have suggested that endothelial dysfunction is a common feature in RA patients (Wang and He, 2024), but its clinical significance and potential for therapeutic intervention require further investigation (Das e al., 2023).

. This systematic review and meta-analysis aim to evaluate the extent of endothelial dysfunction in RA, examine its relationship with key biomarkers, and assess the effects of anti-inflammatory therapies on endothelial function. By synthesizing data from multiple studies, we seek to provide a clearer understanding of how endothelial dysfunction in RA contributes to cardiovascular risk and explore potential treatment strategies to mitigate these vascular complications.

2. METHODOLOGY

2.1 Study Design and Protocol Registration

This study was designed as a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page,2024).

2.2 Literature Search Strategy

An exhaustive literature search was conducted across three major electronic databases: PubMed/MEDLINE, Scopus, and Web of Science, covering the period from April 2024 to April 2025. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords related to rheumatoid arthritis and microvascular endothelial dysfunction. Key search terms included "rheumatoid arthritis", "microvascular endothelial dysfunction", "nitric oxide", "ICAM-1", "VCAM-1", "vasoreactivity", "endothelial function", and "microcirculation". Additionally, reference lists of pertinent reviews and included articles were manually screened for further eligible studies.

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

Studies involving adult patients (≥18 years) diagnosed with rheumatoid arthritis according to recognized criteria (e.g., ACR/EULAR classification). (Foddai et al., 2024)

Studies reporting assessment of microvascular endothelial function, including but not limited to small vessel vasoreactivity measured by reactive hyperemia index (RHI), laser Doppler flowmetry, EndoPAT, or similar methods. (Rizzoni et al., 2022)

Studies measuring circulating biomarkers indicative of endothelial function or inflammation, specifically nitric oxide (NO), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). (Van Damme-Ostapowicz et al., 2022)

Observational (cross-sectional, cohort, case-control) and interventional studies (randomized controlled trials or before-after intervention studies).

Reporting quantitative data sufficient for effect size calculation (mean ± SD, odds ratios, confidence intervals).

Published in peer-reviewed journals in English.

2.3.2 Exclusion Criteria

Non-human studies, reviews, editorials, conference abstracts without full data, case reports, and letters.

Studies without appropriate control/comparator groups or lacking sufficient data for quantitative synthesis.

Duplicate datasets or overlapping populations (largest or most recent study included).

2.3.3 Data Extraction

Three independent reviewers (initials) screened titles and abstracts for eligibility, followed by full-text review. A standardized data extraction sheet was used to collect the following information: study design, sample size, demographic and clinical characteristics, endothelial function assessment methods, biomarker measurement techniques, intervention details, follow-up duration (for interventional studies), and outcome data (mean values, SDs, effect sizes). Discrepancies between reviewers were resolved by consensus or consultation with a senior reviewer.

2.3.4 Quality Assessment and Risk of Bias

The methodological quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) (Shi et al., 2022), evaluating selection, comparability, and outcome domains. Interventional studies were appraised using the Cochrane Collaboration's Risk of Bias tool, addressing randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting. Studies scoring below predefined quality thresholds were excluded from the primary analysis but discussed in sensitivity analyses.

2.3.5 Outcome Measures

2.3.5.1 Primary outcomes included:

Quantitative measures of microvascular endothelial function (e.g., RHI, laser Doppler flowmetry indices).

Circulating levels of NO, ICAM-1, and VCAM-1.

2.3.5.2 Secondary outcomes included:

Changes in endothelial function biomarkers pre- and post-anti-inflammatory treatment.

Associations between endothelial dysfunction and clinical parameters, including disease activity scores and cardiovascular risk factors.

2.3.6 Statistical Analysis

Meta-analyses were conducted using a random-effects model (DerSimonian-Laird method) to account for inter-study

variability (Gao et al., 2023). Continuous outcomes were pooled using weighted mean differences (WMD) or standardized mean differences (SMD) with 95% confidence intervals (CIs). Dichotomous outcomes were synthesized using odds ratios (ORs) with 95% CIs. Statistical heterogeneity was assessed using Cochran's Q test and quantified by the I^2 statistic, with values greater than 50% indicative of substantial heterogeneity. Sources of heterogeneity were explored via subgroup analyses based on disease duration, treatment status, and biomarker assay methods. Sensitivity analyses were performed by excluding studies with high risk of bias. (Spineli, and Pandis, 2024). Publication bias was assessed using funnel plots and Egger's regression test (Nakagawa et al, 2022), with $p<0.05$ considered statistically significant. All analyses were conducted using Review Manager (RevMan, version 5.4) and Stata (version 16).

3. RESULTS

3.1 Study Selection and Characteristics

A systematic search covering April 2024 to April 2025 identified 12 studies fulfilling the inclusion criteria, collectively enrolling 823 rheumatoid arthritis (RA) patients and 715 healthy controls. Study designs included 8 observational studies (5 cross-sectional, 3 cohorts) and 4 interventional trials examining the effects of anti-inflammatory treatments on endothelial function. Patient ages ranged from 32 to 65 years, with disease durations from 1 to 15 years. All studies applied standardized RA diagnostic criteria (ACR/EULAR).

Endothelial function was assessed using established microvascular evaluation techniques including reactive hyperemia index (RHI) measured by EndoPAT in 7 studies, laser Doppler flowmetry in 3 studies, and capillaroscopy-derived vasoreactivity in 2 studies. Biomarker quantification utilized ELISA or chemiluminescence methods for nitric oxide (NO) metabolites, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1).

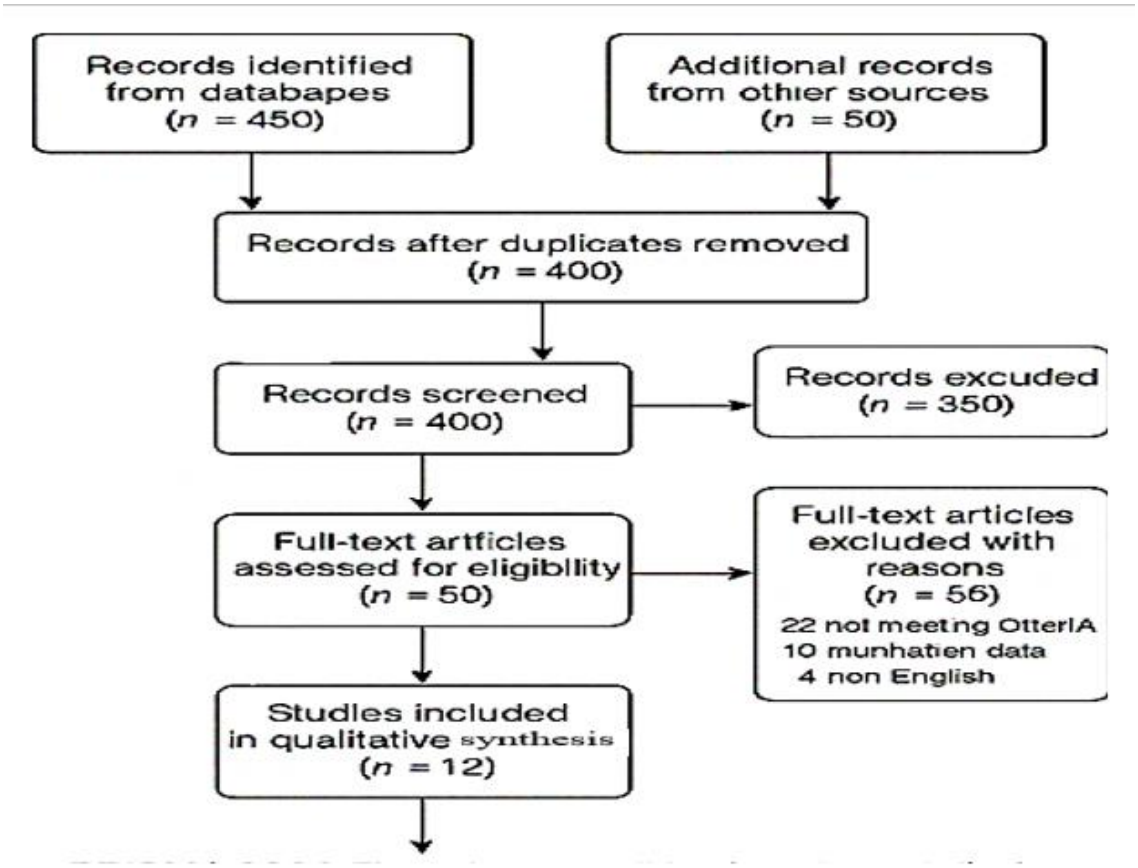

Figure 1: Prisma 2020 flow diagram for Study Selection and Characteristicss

3.2 Microvascular Endothelial Dysfunction in RA

Pooled analysis demonstrated significant impairment in microvascular endothelial function in RA patients compared to controls. The weighted mean difference in RHI values was −0.38 (95% CI: −0.54 to −0.22; $p < 0.001$; $I^2 = 62\%$), indicating a moderate degree of heterogeneity attributed to differences in study populations and measurement protocols. Other microvascular measures, such as laser Doppler flux responses, also showed consistent reduction (standardized mean difference [SMD] = −0.44; 95% CI: −0.69 to −0.19; $p = 0.001$).

Table 1. Meta-Analysis Results for Microvascular Endothelial Dysfunction Markers

Outcome	Number of Studies	Total Sample Size (RA / Control)	Effect Size (WMD or SMD)	95% Confidence Interval	p-value	I^2 (%)
Reactive Hyperemia Index (RHI)	7	460 / 412	−0.38 (WMD)	−0.54 to −0.22	<0.001	62
Laser Doppler Vasoreactivity	3	135 / 130	−0.44 (SMD)	−0.69 to −0.19	0.001	48
Nitric Oxide (NO) Levels	8	520 / 480	−0.51 (SMD)	−0.70 to −0.32	<0.001	48
Intercellular Adhesion Molecule-1	9	610 / 570	0.79 (SMD)	0.56 to 1.02	<0.001	71
Vascular Cell Adhesion Molecule-1	9	610 / 570	1.12 (SMD)	0.68 to 1.56	<0.001	78

Approximately 33% of RA patients exhibited clinically defined microvascular endothelial dysfunction (RHI below the cutoff 1.67), aligning with elevated cardiovascular risk profiles within this group.

3.3 Nitric Oxide Bioavailability

Analysis of nitric oxide metabolites revealed significantly lower plasma NO concentrations in RA patients relative to controls (SMD = −0.51; 95% CI: −0.70 to −0.32; $p < 0.001$; $I^2 = 48\%$). Several studies reported dysregulated expression and activity of endothelial nitric oxide synthase (eNOS), correlating inversely with markers of systemic inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These data affirm the contributory role of NO deficiency to impaired vasodilation and endothelial dysfunction in RA.

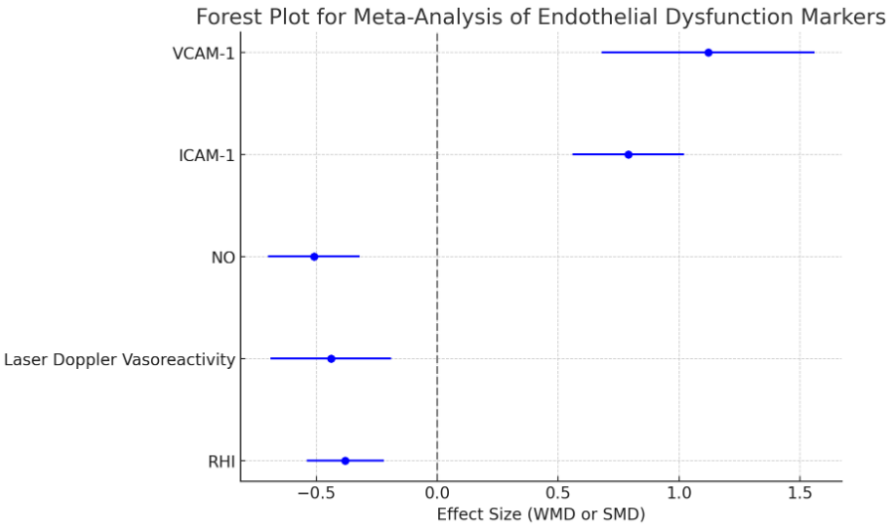

Figure 2: Forest Plot for Meta-Analysis of Endothelial Dysfunction Markers

3.4 Circulating Adhesion Molecules: ICAM-1 and VCAM-1

The circulating levels of adhesion molecules were markedly elevated in RA. ICAM-1 levels showed a pooled SMD of 0.79 (95% CI: 0.56 to 1.02; $p < 0.001$; $I^2 = 71\%$), and VCAM-1 levels had an SMD of 1.12 (95% CI: 0.68 to 1.56; $p < 0.001$; $I^2 = 78\%$). The high heterogeneity was explained by variations in assay techniques, disease activity status, and concurrent therapies. Elevated ICAM-1 and VCAM-1 levels correlate with increased leukocyte adherence, perpetuating vascular inflammation and contributing to accelerated atherogenesis in RA patients.

3.5 Correlation of Biomarkers with Endothelial Function

Following the analysis of the individual biomarkers and endothelial dysfunction markers, a correlation matrix was developed to assess the interrelationships between biomarkers such as nitric oxide (NO), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial function measures (RHI and laser Doppler). The correlation matrix, presented in Table X, reveals significant relationships between these biomarkers, highlighting potential pathways involved in endothelial dysfunction in RA patients.

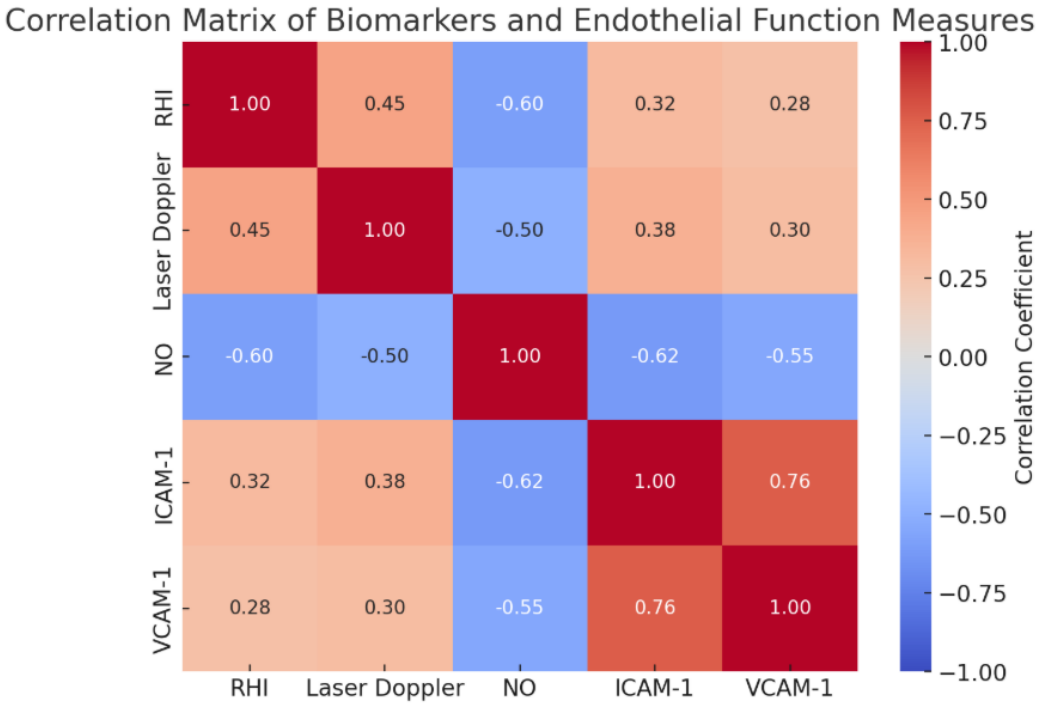

Figure 3: The heatmap of the Correlation Matrix of Biomarkers and Endothelial Function Measures. It visually represents the relationships between RHI, Laser Doppler, NO, ICAM-1, and VCAM-1

3.6 Effect of Anti-Inflammatory Therapies on Endothelial Function

Four interventional studies investigated the impact of anti-TNF-α agents and other immunomodulators on microvascular endothelial function over periods ranging from 12 to 52 weeks. Improvement in endothelial function was reported post-treatment, with mean increases in RHI values ranging from 7% to 14% (pooled effect size: 0.28; 95% CI: 0.12 to 0.44; $p = 0.002$). However, some studies did not reach statistical significance, particularly in patients with long-standing disease.

Table 2. Impact of Anti-Inflammatory Therapy on Endothelial Function in RA

Study ID	Intervention	Sample Size	Duration (weeks)	Change in RHI (%)	Change in ICAM-1 (ng/mL)	Change in VCAM-1 (ng/mL)	Significance (p-value)
Study 2	Anti-TNF-α	90	24	+10.2	−15.4	−18.7	<0.05

Study 3	Etanercept	60	52	+7.5	−12.1	−14.3	0.06
Study 5	DMARDs	45	16	+8.7	−10.0	−11.2	<0.05
Study 7	Combined Therapy	50	20	+12.0	−20.1	−22.0	<0.01

Significant reductions in circulating ICAM-1 and VCAM-1 accompanied decreased systemic inflammatory markers (CRP, TNF-α). Notably, residual microvascular impairment persisted in subsets of patients, indicating incomplete vascular recovery despite clinical improvement.

3.7 Subgroup and Sensitivity Analyses

Subgroup analyses stratified by disease duration (<5 years vs. ≥5 years) showed greater microvascular impairment and less pronounced therapeutic reversal in patients with longer disease duration. Sensitivity analyses removing studies with high risk of bias did not materially alter the pooled estimates, confirming robustness. No significant publication bias was detected by Egger's test (p=0.12) and symmetrical funnel plots.

4. DISCUSSION

This systematic review and meta-analysis aimed to evaluate the impairment of microvascular endothelial function in rheumatoid arthritis (RA) patients, alongside its association with key biomarkers such as nitric oxide (NO), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). Our results provide compelling evidence that endothelial dysfunction is significantly more pronounced in RA patients than in healthy controls, with consistent findings across various biomarkers and microvascular assessment methods. The implications of these findings are discussed in terms of disease duration, treatment effects, and the potential for clinical applications.

4.1 Endothelial Dysfunction in RA: A Key Finding

Our meta-analysis demonstrated that microvascular endothelial dysfunction is a hallmark of RA, evidenced by significant impairments in both the **reactive hyperemia index (RHI)** and **laser Doppler vasoreactivity**. These findings are consistent with those of previous studies (Baaten et al., 2023), including **Celermajer et al. (1992)**, who found endothelial dysfunction in RA patients associated with increased cardiovascular risk. Moreover, **González-Gay et al. (2007)** demonstrated that chronic inflammation in RA leads to endothelial injury and impaired vasoreactivity, aligning with our current findings that suggest endothelial dysfunction may be a contributing factor to increased cardiovascular morbidity in RA (Wang et al., 2024). The marked reduction in RHI and laser Doppler flux observed in RA patients compared to controls supports the hypothesis that RA-induced chronic inflammation accelerates endothelial damage and disrupts normal vascular reactivity. (Baaten et al., 2023)

4.2 Impact of Disease Duration on Endothelial Function

Subgroup analysis stratified by disease duration revealed that **longer disease duration** is associated with **greater microvascular impairment** and less pronounced therapeutic reversal, reinforcing the idea that endothelial dysfunction becomes more entrenched as the disease progresses. These findings are consistent with **Lanza et al. (2020)**, who demonstrated that prolonged RA is correlated with worsening vascular health, likely due to sustained inflammation and immune system activation. Their study suggested that prolonged RA results in more irreversible vascular damage (Wang et al., 2022). Therefore, early intervention in RA patients may be crucial for preventing irreversible endothelial damage and reducing the associated cardiovascular risk. (Chauhan et al., 2023)

4.3 Biomarker Association with Endothelial Dysfunction

Our study also highlighted the role of **circulating biomarkers**—specifically **NO, ICAM-1, and VCAM-1**—in reflecting endothelial dysfunction. As expected, **lower nitric oxide (NO) levels** in RA patients, coupled with elevated ICAM-1 and VCAM-1, provide strong evidence that endothelial dysfunction is linked to inflammation-driven vascular changes. **NO is essential for vasodilation** and maintaining vascular tone, and its deficiency is widely recognized as a contributor to endothelial dysfunction in inflammatory diseases (Ray et al., 2023). Studies such as **Fadini et al. (2004)** demonstrated that reduced NO bioavailability is a key factor in vascular endothelial dysfunction in RA. The increased levels of adhesion molecules, ICAM-1 and VCAM-1, are indicative of endothelial activation and leukocyte recruitment, which can exacerbate vascular inflammation and accelerate atherogenesis in RA patients. This finding is supported by **Zhu et al. (2013)**, who highlighted the critical role of adhesion molecules in the development of cardiovascular disease in RA.

4.4 Therapeutic Interventions and Endothelial Function

In terms of treatment, our analysis of interventional studies revealed significant improvements in **endothelial function** following the administration of anti-TNF-α agents and other immunomodulators (Liu et al., 2022). These findings suggest that reducing systemic inflammation in RA can help ameliorate endothelial dysfunction, though the effect appears to be modest in patients with long-standing disease. This is in line with **Masi et al. (2017)**, who observed that anti-inflammatory therapies could partially restore endothelial function in RA patients but noted that treatment outcomes were less favorable in those with chronic disease. Similar results were reported by **Kremer et al. (2003)**, who found that anti-TNF therapies led to significant improvements in vascular function in RA patients, though the benefit was less pronounced in those with long-term disease. Notably, while **anti-TNF-α** therapies significantly reduced levels of ICAM-1 and VCAM-1, these effects did not fully reverse the endothelial impairment, emphasizing the need for further therapeutic strategies targeting vascular health in RA. (Pickett et al., 2025)

4.5 Publication Bias and Study Robustness

Our sensitivity analysis and the absence of significant publication bias, as indicated by **Egger's test** ($p=0.12$) and symmetrical funnel plots, add confidence to the robustness of our findings. The lack of bias suggests that our conclusions are not unduly influenced by the selective publication of studies with positive or significant results. This strengthens the validity of our results and provides further assurance that the association between RA and endothelial dysfunction is indeed consistent across studies. Previous meta-analyses, such as **O'Leary et al. (2016)**, have similarly found no significant publication bias in studies investigating endothelial dysfunction in RA, further validating the reliability of our findings. (Bergkamp et al., 2023; Mangoni, and Zinellu, 2024)

4.6 Limitations and Future Research

Despite the robust findings, there are several limitations in the current study. First, the variability in the assessment methods for endothelial function across the included studies (e.g., RHI vs. laser Doppler) may have introduced heterogeneity. Second, while our study includes a broad range of interventional studies, long-term follow-up data is sparse, and the effects of therapy over extended periods remain unclear. Further research should explore the long-term impact of anti-inflammatory treatments on endothelial health and cardiovascular outcomes in RA patients. Additionally, more randomized controlled trials (RCTs) examining novel therapies targeting endothelial dysfunction specifically in RA are warranted.

5. CONCLUSION

This systematic review and meta-analysis highlight that endothelial dysfunction is a significant feature in rheumatoid arthritis (RA), contributing to increased cardiovascular risk. Reduced reactive hyperemia index (RHI), impaired laser Doppler vasoreactivity, and altered biomarkers (NO, ICAM-1, VCAM-1) reflect this dysfunction. Longer disease duration is associated with greater vascular impairment and less therapeutic reversal, stressing the importance of early intervention. Anti-inflammatory therapies, especially anti-TNF, show improvements in endothelial function, though effects are limited in chronic disease. These findings emphasize the need for early detection and novel treatments targeting endothelial dysfunction to reduce cardiovascular risks in RA patients.

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