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Effects of TNF-α Inhibitors on Subclinical Atherosclerosis and Endothelial Function in Patients with Psoriatic Arthritis: A Systematic Review

Effets des anti-TNF alpha sur l'athérosclérose infraclinique et la fonction endothéliale chez les patients atteints de rhumatisme psoriasique : Revue systématique

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Abstract

Background: Patients with psoriatic arthritis (PsA) are at increased risk of cardiovascular disease (CVD), largely driven by systemic inflammation and accelerated atherosclerosis. Tumor necrosis factor-alpha (TNF-alpha) inhibitors have transformed PsA treatment and may exert vascular protective effects. This systematic review aimed to evaluate the impact of TNF-alpha inhibitors on atherosclerosis and endothelial dysfunction in PsA patients.

Methods: This systematic review followed the preferred reporting items for systematic reviews guidelines. A systematic search of PubMed, Scopus, Cochrane Library and Embase databases was conducted, identifying original articles up to September 3rd, 2024. Outcomes included carotid intima-media thickness (CIMT), endothelial function, carotid plaques, and biomarkers of inflammation, lipid metabolism, and coagulation. This systematic review was registered in prospero (CRD42023451234).

Results: Five studies met the inclusion criteria and were published between 2011 and 2020. TNF-alpha inhibitors were associated with a reduction in CIMT in one study (0.7±0.18 vs 0.8±0.26; p=0.002 for the CCA and 0.94±0.31 vs 1.24±0.52; p<0.001 for the bulb), particularly with longer treatment duration (B:-0.317, p<0.001), while two studies reported progression of CIMT over time. Carotid plaque prevalence was significantly lower in TNF-alpha–treated patients compared to those on csDMARDs (15.8% vs 40.4%; p<0.0001). No consistent improvement in endothelial function, assessed by flow-mediated dilation or reactive hyperemia index was observed. TNF-alpha inhibitors consistently reduced inflammatory markers (CRP, ESR) and some lipid parameters (LDL-C, triglycerides). One study showed significant improvement in fibrinolytic and hemostatic markers (p<0.001), especially among patients achieving minimal disease activity (p<0.005).

Conclusion: TNF-alpha inhibitors may offer vascular benefits in PsA by attenuating subclinical atherosclerosis and systemic inflammation. However, their effects on endothelial function remain unclear. Further large-scale, controlled, and long-term studies are warranted to confirm their cardioprotective role and define their impact on clinical cardiovascular outcomes in PsA patients.

Keywords: Psoriatic arthritis, atherosclerosis, endothelial dysfunction, inflammation, TNF-alpha inhibitors

Résumé

Introductions : Les patients atteints de rhumatisme psoriasique (RPso) présentent un risque accru de maladies cardiovasculaires (MCV), principalement en raison de l'inflammation systémique et de l"athérosclérose. Les inhibiteurs du facteur de nécrose tumorale alpha (TNF-α) ont transformé la prise en charge du RPso et pourraient exercer des effets vasculoprotecteurs. Cette revue systématique avait pour objectif d'évaluer l'impact des inhibiteurs du TNF-α sur l'athérosclérose et la dysfonction endothéliale chez les patients atteints de RPso.

Méthodes : Cette revue systématique a été conduite selon les recommandations PRISMA. Une recherche systématique a été effectuée dans les bases de données PubMed, Scopus, Cochrane Library et Embase, incluant les articles originaux publiés jusqu'au 3 septembre 2024. Les critères de jugement comprenaient l'épaisseur intima-média carotidienne (CIMT), la fonction endothéliale, la présence de plaques carotidiennes, ainsi que les biomarqueurs de l'inflammation, du métabolisme lipidique et de la coagulation. Cette revue systématique a été enregistrée sur PROSPERO (CRD42023451234).

Résultats : Cinq études, publiées entre 2011 et 2020, répondaient aux critères d'inclusion. Les inhibiteurs du TNF-α étaient associés à une réduction de la CIMT dans une étude (0,7 ± 0,18 vs 0,8 ± 0,26 ; p = 0,002 pour la carotide commune et 0,94 ± 0,31 vs 1,24 ± 0,52 ; p < 0,001 pour le bulbe carotidien), notamment avec une durée de traitement plus longue (B : –0,317 ; p < 0,001), tandis que deux études rapportaient une progression de la CIMT au fil du temps. La prévalence des plaques carotidiennes était significativement plus faible chez les patients traités par inhibiteurs du TNF-α comparés à ceux recevant des csDMARDs (15,8 % vs 40,4 %; p < 0,0001). Aucune amélioration constante de la fonction endothéliale, évaluée par la dilatation médiée par le flux ou l'indice d'hyperémie réactive, n'a été observée. Les inhibiteurs du TNF-α réduisaient de manière constante les marqueurs inflammatoires (CRP, VS) et certains paramètres lipidiques (LDL-C, triglycérides). Une étude montrait une amélioration significative des marqueurs fibrinolytiques et hémostatiques (p < 0,001), en particulier chez les patients atteignant une activité minimale de la maladie (p < 0,005).

Conclusion : Les inhibiteurs du TNF-α pourraient conférer des bénéfices vasculaires chez les patients atteints de RPso en atténuant l'athérosclérose infra-clinique et l'inflammation systémique. Cependant, leurs effets sur la fonction endothéliale demeurent incertains. Des études complémentaires, à grande échelle, contrôlées et prospectibes, sont nécessaires pour confirmer leur rôle cardioprotecteur et préciser leur impact sur les événements cardiovasculaires cliniques chez les patients atteints de RPso.

Mots-clés : Rhumatisme psoriasique, athérosclérose, dysfonction endothéliale, inflammation, inhibiteurs du TNF-α.

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory and immune-mediated disease that can variably affect synovial joints, tendons, entheses and axial sites. It develops in up to 30% of patients with established skin and/or nail psoriasis (1). PsA is also associated with systemic effects, notably an increased risk of cardiovascular disease (CVD) (2).

Patients with PsA exhibit a well-established increase in cardiovascular and metabolic risk factors, accelerated atherosclerosis, and a heightened incidence of premature cardiovascular events, such as myocardial infarction and stroke. Chronic systemic inflammation has been identified as a key driver of vascular dysfunction in these patients (3).

TNF-alpha, a pro-inflammatory cytokine, plays a pivotal role in the pathogenesis of PsA and has been implicated in both endothelial dysfunction and atherosclerosis progression. Elevated TNF-alpha levels are linked to increased vascular inflammation, which predisposes patients with PsA to early-onset CVD (4).

Over the past decades, TNF-alpha inhibitors have revolutionized the management of PsA by targeting systemic inflammation. Emerging evidence suggests that these agents may not only reduce joint inflammation but also appear to confer potential benefits in reducing adverse cardiovascular events and mortality in patients with PsA (5).

While the cardiovascular benefits of TNF-alpha inhibitors are well established in rheumatoid arthritis (6), their impact on atherosclerosis in patients with PsA remains less clearly defined. The limited studies conducted to date have reported inconsistent findings, with some suggesting improvements in atherosclerosis-related markers, while others have demonstrated minimal or no benefit (7–11).

Since the last comprehensive systematic review in 2014 (12), no updated synthesis has thoroughly evaluated the effects of TNF-alpha inhibitors on atherosclerosis in patients with PsA. Given the increased cardiovascular risk in these patients, understanding the impact of these biologic therapies on atherosclerotic progression is critical for optimizing patient outcomes.

This systematic review aimed to synthesize the existing evidence on the effect of TNF-alpha inhibitors on atherosclerosis and endothelial dysfunction in patients with PsA.

Methods

All data analyzed were extracted from published studies. A narrative synthesis was used to integrate the findings due to anticipated heterogeneity among the included studies, particularly in terms of study designs, interventions, and outcome measures. For the present paper, no ethical approval or written informed consent was required.

This systematic review was registered in prospero: CRD42023451234. The methodology of the current systematic review is detailled in the protocol (13).

Search strategy

This systematic review followed the preferred reporting items for systematic reviews guidelines (PRISMA) (14). Eligible articles were searched in Pubmed, Scopus, Embase and Cochrane Library. For PubMed, the search was carried out using a strategy employing the combination of the MeSH (Medical Subject Headings) terms associating the synonyms of “psoriatic arthritis”, “tumor necrosis factor alpha inhibitors”, and “atherosclerosis” or “endothelial dysfunction” (Supplementary Table 1). For Scopus, Cochrane Library and Embase, the previous terms were searched in the article title, abstract, or keywords. In addition, the reference lists of the included articles were checked. The two first authors of this systematic review (MY and BH) agreed on the articles to be included in this paper. All the aspects of systematic review methods were predefined prior to initiating the review.

Supplementary Table 1. Mesh terms applied for this systematic review in Pubmed

Synonyms of Psoriatic arthritis	Synonyms of TNF alpha inhibitors	Synonyms of atherosclerosis
«Psoriatic arthritis»[Title/Abstract] OR «PsA»[Title/Abstract]	AND	AND
	«TNF-alpha inhibitors»[Title/Abstract] OR «TNF inhibitors»[Title/Abstract] OR «anti-TNF»[Title/Abstract] OR «TNF blockers»[Title/Abstract] OR «infliximab»[Title/Abstract] OR “Tumor Necrosis Factor- α Blockers” [Title/Abstract] OR «adalimumab»[Title/Abstract] OR «etanercept»[Title/Abstract] OR «golimumab»[Title/Abstract] OR «certolizumab»[Title/Abstract]	«atherosclerosis»[Title/Abstract] OR «subclinical atherosclerosis»[Title/Abstract] OR «carotid intima-media thickness»[Title/Abstract] OR «C-IMT»[Title/Abstract] OR «Intima-Media Thickness”[Title/Abstract] OR «endothelial function»[Title/Abstract] OR «endothelial dysfunction»[Title/Abstract] OR «Atherosclerosis»[All fields] OR «vascular risk factors»[Title/Abstract] OR «VRFs”[Title/Abstract] OR «Atherogenesis»[All fields]) OR «flow-mediated dilation” [Title/Abstract] OR «FMD»[Title/Abstract] OR «arterial stiffness»[Title/Abstract] OR «vascular function»[Title/Abstract] OR «cardiovascular risk»[Title/Abstract] OR «carotid atherosclerotic disease»[Title/Abstract] OR «fibrinolytic changes»[Title/Abstract] OR «fibrinolytic variables»[Title/Abstract]

Selection criteria

Inclusion criteria:
A comprehensive search was conducted from inception until September 3rd, 2024. This review included studies that met the following PICOS criteria: 1) Patients with PsA according to the CASPAR or 2009 ASAS criteria (P), 2) Treated with TNF-alpha inhibitors as the primary treatment intervention (I), 3) Compared to patients receiving other biologics, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), placebo, or before-and-after comparisons within the same cohort (C), 4) The main outcome of interest included atherosclerosis-related measures such as carotid intima-media thickness (CIMT) measurements (mean-max of common carotid artery (mean-max CCA, mm), mean-max of the carotid bifurcation (mean-max bulb, mm), cumulative mean of mean-CIMT (mean-CIMT) and cumulative mean of maximum-CIMT (max-CIMT)), endothelial dysfunction (flow-mediated dilation (FMD)), reactive hyperemia index (RHI), arterial stiffness, and the presence of carotid plaques. The secondary outcomes included atherosclerosis biomarkers (Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), Osteoprotegerin (OPG), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), total cholesterol, LDL cholesterol, triglycerides, homeostatic and fibrinolytic markers.
Only full papers available and written in English were considered. We selected in this systematic review original articles: observational studies (cohort, case-control, cross-sectional) and randomized controlled trials (RCTs) (S). Additional articles were manually retrieved based on the references of selected articles. If any study included overlapping data, the most comprehensive one was selected.

Exclusion criteria:
1) Studies were excluded if they did not report direct measurements of atherosclerosis or endothelial dysfunction. 2) Papers written in languages other than English. 3) Publications not representing original research (i.e.; reviews, editorials, qualitative papers, case reports, and letters to editors) were excluded. Articles not in compliance with the systematic review purpose were excluded.

Study Selection Process

The search strategy, literature selection, and data extraction were conducted independently by two investigators (MY and BH), using a pre-piloted data extraction form, then discussed. The selection of studies was carried out in two stages: Stage 1: Initial Screening where the reviewers assessed titles and abstracts against the eligibility criteria. Studies that clearly did not meet inclusion criteria were excluded at this stage, Stage 2: Full-Text Review, during which full-text articles were retrieved for studies that met the initial screening criteria. Both reviewers independently assessed the full text for inclusion, and any discrepancies were resolved by a third reviewer (BH). The extracted data included the main methodological characteristics of the articles: study data (year of publication, country, study design, number and mean age of included subjects, inclusion and exclusion criteria, duration of the follow-up), population characteristics (age, gender, PsA severity, and comorbidities), intervention details (type and dosage of TNF-alpha inhibitor, frequency of administration) as well as outcomes data.

Quality of the studies and risk of bias assessment

To evaluate the methodological quality of the included studies, we used Methodological items for non-randomized studies (MINORS) for observational studies and Consolidated Standards of Reporting Trials (CONSORT) for randomized trials (15,16). Furthermore, we identified potential biases using Newcastle Ottawa Scale (NOS) for the cohort and case control studies and the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (17,18). Only studies that met high-quality criteria belonged to our final selection.

Results

Study Selection

The current systematic review encompassed a total of 5 articles, selected from an initial pool of 635 papers identified through a search process outlined in the PRISMA flow diagram (Fig 1).

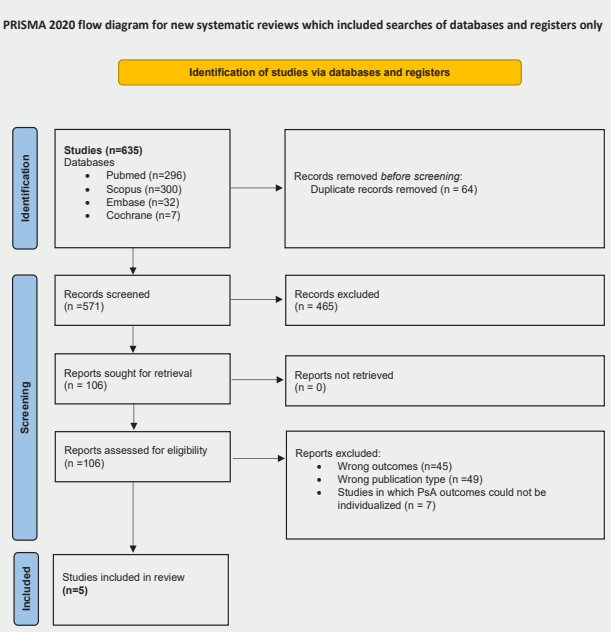

Figure 1. PRISMA flow diagram

Study Characteristics

The main characteristics of the 5 studies retained in this systematic review are represented in Supplementary Table 2. The studies, published between 2011 and 2020 (7,8), were conducted across various countries, including Italy (7–10) and Norway (11). The included studies consisted of 5 observational studies with prospective (7–11) and control-group (7,10) designs.

Supplementary table S2. Main characteristics and results of the selected studies aiming to assess the effect of TNF alpha inhibitors on atherosclerosis in psoriatic arthritis patients: a systematic review

First author (ref) Year of publication Country	Study design/ Characteristics of the population studied	Inclusion, exclusion criteria	Methods of evaluation	Cardiovascular disease parameters	Main outcomes	Conclusion of the authors
Ortolan et al. 2020 Italy	Cohort study Cases: 32 (51±8)	*Inclusion* .PsA patients according to the CASPAR criteria . Inadequate response or intolerant to CsDMARDs and treated with anti-TNF-α .None concomittant use of DMARDs. . Sporadic NSAIDs or low-dose glucocorticoid less than1 week per month allowed *Exclusion* .Glomerular filtration rate <60 ml/min, diabetes mellitus .Pre-existing coronary artery disease, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease .Treatment for metabolic syndrome (e.g. statins, antihypertensive or hypoglicaemic drugs), active smokers.	*Period of evaluation* *at baseline (T0), 2 years (FU1) and 5 years (FU2) of treatment* *Parameters evaluated* .Disease activity parameters: TJ, SJ, PASI, (DAS)-28, MDA .Atherosclerosis biomarkers: hs-CRP, OPG, TC, LDL-C Total cholesterol (TC), low-density and high-density lipoproteins (LDL-C, HDL-C), triglycerides (TG), blood glucose, C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), TNF-α and osteoprotegerin (OPG) .Blood pressure: SBP, DBP	*Arterial structural* *Properties. B-mode ultrasound* .carotid intima-media thickness (mean-IMT) .maximum IMT (M-MAX) in each segment (common, bulb, internal), bilaterally. *Endothelial function* post-occlusion flow-mediated dilation (FMD) of the brachial artery using high-sensitivity ultrasonography. B-mode scan of the right brachial artery in longitudinal section above the elbow	. AT FU2 : IMT-mean and M-max did not change significantly (0.9±0.3 and 1.1±0.3, p=ns). . No significant variation in FMD values was observed during the study period. .SBP remained stable throughout the follow-up .DBP decreased significantly from FU1 to FU2 (80±10 vs. 74±7 mmHg, p=0.001). . Significant decrease of DAS28 and CRP was observed at FU1 and preserved at FU2 (DAS28 2.4±0.9, CRP 2.73±2.51; p=ns vs. FU1). .Hs-CRP, OPG, TC, LDL-C decreased at FU1, and remained stable at FU2 .Fasting glucose slightly increased at FU1 but then tended to stabilise at FU2 .Triglycerides decreased at FU1, and then increased back at FU2 .No significant difference was observed in HDL-C levels throughout the study period. .No major CV events were observed over the 5-year period in our low-risk population	. A slight progression of subclinical atherosclerosis in PsA was observed in the first 2 years of anti- TNF-α treatment. This process seemed to decelerate in follow-up extension to 5 years.
Ramonda et al. 2014 Italy	Cohort study Cases: 32 (51±8) September 2011 to June 2012.	*Inclusion* .PsA patients according to the CASPAR criteria . Inadequate response or intolerant to CsDMARDs and treated with anti-TNF-α .None concomittant use of DMARDs. . Sporadic NSAIDs or low-dose glucocorticoid less than1 week per month allowed *Exclusion* .Glomerular filtration rate <60 ml/min, diabetes mellitus .Pre-existing coronary artery disease, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease .Treatment for metabolic syndrome (e.g. statins, antihypertensive or hypoglicaemic drugs), active smokers.	*Period of evaluation* *at baseline (T0), 2 years of treatment* *Parameters evaluated* .Disease activity parameters: TJ, SJ, (DAS)-28 .Atherosclerosis biomarkers: hs-CRP, OPG, TC, LDL-C Total cholesterol (TC), low-density and high-density lipoproteins (LDL-C, HDL-C), triglycerides (TG), blood glucose, TNF-α, OPG, (IL)-6, and VEGF .Blood pressure: SBP, DBP	*Arterial structural* *Properties. B-mode ultrasound* .carotid intima-media thickness (mean-IMT) .maximum IMT (M-MAX) in each segment (common, bulb, internal), bilaterally. *Endothelial function* post-occlusion flow-mediated dilation (FMD) of the brachial artery using high-sensitivity ultrasonography. B-mode scan of the right brachial artery in longitudinal section above the elbow	.Mean-IMT and M-Max were significantly higher than at baseline 0.75 ± 0.12 vs 0.95 ± 0.39 and 0.90 ± 0.23 vs 1.08 ± 0.43 P < 0.0005) FMD was unmodified: 5.8 ± 2.1 vs 5.3 ± 1.6 ns SBP and DBP did not vary during the study period. CRP (P < 0.01) and OPG (P = 0.011) serum levels were significantly decreased while serumTNF- _ levels increased (P = 0.0003); IL-6 and VEGF were not modified	Despite improvement in clinical status, arterial remodelling was observed in the PsA patientswho were treated with anti TNF- _ agents for two years.

Supplementary table S2. (following) Main characteristics and results of the selected studies aiming to assess the effect of TNF alpha inhibitors on atherosclerosis in psoriatic arthritis patients: a systematic review

First author (ref) Year of publication Country	**Study design/ Characteristics of the population studied**	**Inclusion, exclusion criteria**	**Methods of evaluation**	**Cardiovascular disease parameters**	**Main outcomes**	**Conclusion of the authors**
Deyab et al. 2017 Norway	Observational study 29 PsA patients Mean age: 50 [23-78]	Inclusion criteria: - Males and females with an age range 18–80 years - PsA according to the Moll and Wright 1973 criteria - Clinical indication for starting with either MTX monotherapy or anti-TNF treatment with or without MTX comedication (anti-TNF ± MTX). Exclusion criteria: -Lack of cooperability, anycontraindication for MTX and anti-TNF - Any significant infection (including subclinical tuberculosis), pregnancy or breastfeeding, congestive heart failure, use of systemic glucocorticoids > 10 mg/ day during the last 2 weeks or anti-TNF during the last 4 weeks before the inclusion - Any chronic inflammatory disease other than RA, AS, or PsA.	Period of evaluation: At baseline and after 6 weeks and 6 months of treatment. Parameters evaluated: -Disease activity: CRP, ESR, BASDAI, BASFI, PtGA, PGA, MHAQ -Cardiovascular risk factors: Hypertension, BMI, hyperlipidemia, current smoking, family history of CVD or death, diabetes -Medical history: Previous myocardial infarction, angina pectoris	Endothelial Function -Reactive hyperemia peripheral arterial tonometry (RH-PAT) examination which evaluates the overall health of the endothelium by measurment of finger arterial pulsatile volume changes. -Reactive Hyperemic Index (RHI): ratio between the magnitude of the average postobstructive pulse wave amplitude (PWA) and the average of baseline PWA (preocclusion). Endothelial Dysfunction was defined as RHI ≤ 1.67 as recommended by the manufacturer and in accordance with findings from a population at risk for ischemic heart disease	. The PsA group showed RHI improvement at both visits (RHI at 6 weeks = 1.67 and RHI at 6 months = 1.80). . None of the RHI changes in the PsA group reached statistical significance. . In both treatment groups, RHI significantly improved at both follow-up visits compared to baseline (MTX: baseline to 6 weeks p = 0.002, baseline to 6 months p = 0.001; anti-TNF ± MTX: baseline to 6 weeks p = 0.004, baseline to 6 months p = 0.024). After 6 months of treatment, RHI values in the MTX group continued to increase compared to 6 weeks. However, in the anti-TNF ± MTX group RHI values at 6 months were lower than at 6 weeks, resulting in a statistically significant difference in RHI values between the two groups at 6 months. Within the RA and PsA groups there were no significant differences in RHI between patients treated with MTX and anti-TNF ± MTX. .The difference in RHI change from baseline to 6 months between the MTX group and the anti-TNF ± MTX group remained statistically significant after adjustments for age, female gender, rheumatic disease duration, and IA diagnosis In analyses adjusted for baseline RHI values, MTX was associated with a greater improvement in RHI than antiTNF ± MTX after 6 months in patients with ED (p = 0.007).	Treatment with MTX and anti-TNF ± MTX was associated with a relatively fast improvement of EF in IA patients with ED, independent of change in disease activity. After 6 months, the EF improvement was more pronounced in the MTX group than in the anti-TNF ± MTX group. No statistical differences were demonstrated in the PsA group.
Di-Minno Et al 2011 Italy	Cross-sectional Comparative study (June 2009-January 2010) *Case group:224 PsA patients:* .Age: 52.61 ± 11.37. .120 on TNF-blockers for ≥ 1 year. .104 on traditional DMARD for ≥1 year. *control group: 305* matched subjects without inflammatory or rheumatologic disease	*Inclusion :* .PsA patients fulfilling CASPAR criteria. .Clinically active disease. .None of the subjects in the case group were on NSAIDs or prednisone at the time of the study, nor were any of them receiving combined treatments (TNF-blockers, DMARDs). *Exclusion:* .Age <18 years. .High-grade carotid stenosis or a history of carotid surgery/ stenting. .Familial hypercholesterolemia/ hypertriglyceridemia. .NYHA class III/IV heart failure, arrhythmia, recent vascular events or venous thrombosis.	*Period of evaluation:* No baseline/No follow-up US assessment Timing: performed once per patient during the 6-month enrollment *Parameters evaluated* .Disease activity parameters: PGA, BASDAI, DAS28, ESR, CRP, interleukin 6 .Vascular risk factors (VRFs): Fasting glucose, Blood pressure, total cholesterol (TC), low high-density lipoproteins (HDL-C), triglycerides (TG), waist circumference. Patients were defined as having a MetS if 3 or more of these VRFs were present.	The subjects underwent a bilateral carotid ultrasonography with measurements of the common carotid artery (CCA) and carotid bifurcation (bulb) in multiple projections (anterior, lateral and posterior). *.Carotid intima-media thicnkness (C-IMT) Measurements:* .The CCA-IMT .mean-maxCCA .mean-maxBulb *.presence of carotid plaques*	.PsA patients without VRFs had higher C-IMT versus 40.4% than controls (p<0.0001). .C-IMT was lower in PsA patients on TNF blockers vs DMARDs (p<0.0001). .Treatment duration inversely predicted C-IMT in TNF blockers group (β= -0.317, P<0.0001). .Carotid plaques were found in 15.8% in patients on TNF blockers (vs 40.4% in patients on DMARDs; p<0.0001). . The presence of carotid plaques was inversely correlated with TNF blockers duration (*r*= -0.206, *p*=0.024). . No significant correlation were found between disease duration and these parameters: C-IMT and the presence of carotid plaques. .The MetS was not associated with differences in C-IMT in subjects on TNF- blockers.	.The study suggests that TNF-blockers are more effective in reducing subclinical atherosclerosis and improving cardiovascular outcomes in PsA patients. . PsA patients on TNF-α blockers had lower C-IMT and fewer carotid plaques compared to those on traditional DMARDs.

Supplementary table S2. (following) Main characteristics and results of the selected studies aiming to assess the effect of TNF alpha inhibitors on atherosclerosis in psoriatic arthritis patients: a systematic review

First author (ref) Year of publication Country	**Study design/ Characteristics of the population studied**	**Inclusion, exclusion criteria**	**Methods of evaluation**	**Cardiovascular disease parameters**	**Main outcomes**	**Conclusion of the authors**
Di-Minno Et al. 2014 Italy	Prospective comparative study (January 2010–January 2012). *Case group:* 76 PsA patients with active disease switching to TNF blockers. .Age: 45.73 ± 12.35 .Adalimumab (n=16) .Etanercept (n=24) .Infliximab (n=36) *control group:80 PsA* matched subjects with minimal disease activity (MDA) on tradiotional DMARDs	*Inclusion :* .PsA patients fulfilling CASPAR criteria .Non-responders to DMARDs (Group 1) or achieving MDA (Group 2). *Exclusion:* .History of thrombosis, antiphospholipid antibodies, chronic infectious disease (including hepatitis B and C) or conditions affecting hemostasis. .Previous treatment with TNF-a blockers.	*Period of evaluation* At baseline (T0) and after 6 months of treatment. *Parameters evaluated* . Vascular risk factors (VRF): (obesity, HTN, impaired fasting glucose, hypercholesterolemia, and hypertriglyceridemia). . Disease activity parameters: TJC, SJC ,tender entheseal count, PASI, HAQ,VAS score, ESR, CRP, Subjects were classified as having achieved MDA when fulfilling 5 of the following 7 outcome measures at 6-month followup (T1): TJC ≤ 1, SJC ≤ 1, PASI ≤ 1 or body surface area ≤ 3, VAS for pain ≤15, patient global disease activity VAS score of ≤ 20, HAQ ≤ 0.5, and tender entheseal points ≤ 116. Otherwise, they were considered as not having achieved MDA (no-MDA). .	At baseline (T0) and after 6 months of treatment: .*Hemostatic variables* (fibrinogen, D-dimer, FVII, FVIII, vWF). .*Fibrinolytic variables* (PAI-1, t-PA, PAI-1/t-PA ratio). .*Inflammatory markers* (CRP, ESR).	.After 6 months of follow-up, 27 (35.5%) of case group 76 achieved MDA. *Effect of TNF-α Inhibitors on Hemostatic and Fibrinolytic Variables:* . Patients with PsA treated with TNF-α inhibitors (Group 1) showed significant improvements in hemostatic and fibrinolytic variables after 6 months, unlike those on traditional DMARD (Group 2): In Group 1, changes were significant for PAI-1 ($p < 0.001$), t-PA ($p < 0.001$), fibrinogen ($p < 0.001$), D-dimer ($p < 0.001$), FVIII ($p < 0.001$), vWF ($p < 0.001$), protein C ($p < 0.001$), protein S ($p < 0.001$), and antithrombin ($p = 0.031$). No significant changes were observed in Group 2 ($p > 0.05$ for all variables). . TNF-α blockers significantly reduced prothrombotic markers thand DMARD (e.g., Δ-percentage fibrinogen: −15.2% vs. −1.3%; $p < 0.001$). . TNF-α inhibitors significantly reduced levels of fibrinolytic markers (PAI-1, t-PA) and acute-phase proteins (D-dimer, FVIII, vWF) compared to DMARD ($p < 0.001$ for all comparisons between Group 1 and Group 2). .Among TNF-α-treated patients, those achieving MDA had greater reductions in hemostatic/ fibrinolytic variables than non-MDA patients ($p < 0.05$ for all). .MDA achievement maximally impacted fibrinolytic variables: PAI-1 ($\beta = 0.691$; $p < 0.001$) and t-PA ($\beta = 0.326$; $p = 0.004$). *Inflammation and Hemostatic Changes:* .Δ-percentage CRP reduction is correlated with improvements in these parameters: PAI-1 ($r = 0.326$, $p = 0.004$), PAI-1/t-PA ratio ($r = 0.283$, $p = 0.013$), and D-dimer ($r = 0.250$, $p = 0.029$). *Multivariate Analysis:* TNF-α treatment independently predicted improvements in fibrinolytic (PAI-1, t-PA) and coagulation (D-dimer, FVIII, vWF) variables (all $p < 0.01$).	.TNF-α inhibitors improve hemostatic and fibrinolytic balance in PsA patients, particularly in those achieving MDA. .Maximal effects were seen in fibrinolytic variables (PAI-1, t-PA) and acute-phase proteins (D-dimer, FVIII, vWF).

Exclusion criteria were explicitly stated in all studies, with common criteria including the presence of a glo¬merular filtration rate <60 ml/min (8,9), diabetes mellitus (8,9), pre-existing coronary artery disease, cerebrovascular acci¬dent, transient ischaemic attack or pe-ripheral vascular disease (7–9,11), familial hypercholesterolemia/ hypertriglyceridemia (7), any significant infection (including subclinical tuberculosis) (10,11), pregnancy or breastfeeding (10,11), use of systemic glucocorticoids >10 mg/day during the last 2 weeks or anti-TNF during the last 4 weeks before the inclusion (7,10,11), treatment for metabolic syndrome (e.g. statins, anti¬hypertensive or hypoglicaemic drugs) and active smoking (8), immunologic disorders other than PsA, rheumatoid arthritis (RA) (10,11), conditions known to affect hemostatic variable levels (10).

Characteristics of the patients

The main characteristics of the patients are represented in Supplementary Table 2.
The sample sizes of the studied group ranged from 29 to 224 participants (7,11). The majority of the studies involved patients diagnosed with PsA based on the CASPAR criteria (7–10) and one study according to the 1973 Moll and Wright criteria (11). The study by Deyab et al. also included patients with RA (n = 64) and AS (n = 20) (11). The sample size of the control group ranged from 98 and 305 (7,10). The mean age of the PsA groups was 50 years [45.7-52.6] (7,10). The duration of follow up was 6 weeks (11), 6 months (7,10,11), 2 years (9), and 5 years (8). One study had a cross-sectional design. Therefore, no follow-up was conducted (7). The distribution of the patients according to the type of anti TNF-alpha agent was described in 4 articles (7–10). The most prescribed TNF-alpha blocker was Etanercept (n=81) followed by Adalimumab (n=74), and infliximab (n=73).

Risk of Bias Assessment

The risk of bias assessment indicated that all these studies were at low risk of bias. The detailed risk of bias evaluations, categorized by study design, are summarized in Supplementary Table 3.

Supplementary table S3:
Quality of the studies using MINORS

	Ortolan et al. 2020	Ramonda et al. 2014	Di Minno et al. 2011	Di Minno et al. 2014	Deyab et al. 2017
A clearly stated aim	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2
Prospective collection of data	2	2	1	2	2
Endpoints appropriate to the aim of the study	1	1	2	2	2
Unbiased assessment of the study endpoint	0	0	2	1	0
Follow-up period appropriate to the aim of the study	2	1	-	2	1
Loss to follow up less than 5%	2	2	-	0	2
Prospective calculation of study size	0	0	2	0	0
An adequate control group	-	-	2	2	-
Contemporary groups	-	-	2	2	-
Baseline equivalence of groups	-	-	1	1	-
Adequate statistical analyses	-	-	2	2	-
Score	11/16	11/16	18/20	18/24	11/16
Interpretation	Moderate Quality	Moderate Quality	High quality	Good Quality	Moderate Quality

Risk of Biais using New castle Ottawa scale (cohort)

	Selection				Comparability	Outcome			Risk of biais
	1	2	3	4	5	6	7	8	
Ortolan et al.2020	b	a	a	a	0	b	a	b	7 (High Quality/Low risk of biais)
Ramonda et al.2014	b	a	a	a	0	b	a	b	7 (High Quality/Low risk of biais)
Di Minno et al. 2014	a	a	a	a	b	a	a	c	7 (Good Quality/Low risk)
Deyab et al. 2017	b	a	a	a	a	d	b	a	6

Risk of Biais using New castle Ottawa scale (case –control)

	Selection				Comparability	Outcome			Risk of biais
	1	2	3	4	5	6	7	8	
Di Minno et al.2011	a	a	a	a	b	a	a	c	7 (good quality/ Low risk)

Effect of TNF-alpha inhibitors on atherosclerosis-Related Measures

Carotid Intima-Media Thickness (CIMT)

Three studies measured the effect of TNF-alpha inhibitors on CIMT in PsA patients (7–9). According to Di Minno et al., CIMT was significantly lower in PsA patients on TNF-alpha blockers compared to those on csDMARDs (p<0.0001). Both mean-max values of CCA (mm) and bulb (mm) were lower when compared to the control group (0.7±0.18 vs 0.8±0.26; p=0.002 for the CCA and 0.94±0.31 vs 1.24±0.52; p<0.001 for the bulb). Among TNF-alpha inhibitors, adalimumab showed the strongest association with reduced mean-max CCA and bulb thickness, followed by etanercept and infliximab (7). In this study, longer exposure to TNF-alpha blockers was associated with lower CIMT (mean-max CCA: r=-0.319, p<0.001, mean-max bulb: r=-0.296; p=0.001). In the linear regression model, treatment duration significantly predicted CIMT improvement in patients on TNF-alpha inhibitors (B:-0.317, p<0.001). However, findings from Ramonda et al. and Ortolan et al. showed that CIMT progressed after two years of follow-up (8,9) (Table 1).

Table 1. Overview of eligible studies on effects of TNF inhibitors on Subclinical Atherosclerosis and Endothelial Function in Patients with Psoriatic Arthritis

First author	Primary outcomes			Secondary outcomes	
	Carotid intima media thickness	Endothelial function	Carotid plaques	Inflammatory markers Lipid profile	Homeostatic and Fibrinolytic function
Di-Minno et al. 2011 [7]	TNF blockers vs DMARDs: **Mean-max CCA (mm):** 0.7 ±0.18 vs 0.8±0.26; p =0.002). **Mean-max bulb (mm):** 0.94±0.31 vs 1.24±0.52; p<0.001). Treatment duration inversely predicted C-IMT in TNF blockers group (β= -0.317, P<0.0001). No significant correlation between disease duration and CIMT parameters (p=0.954 for mean-max CCA and p=0.904 for mean-max bulb).	—	15.8% (n=19) in patients on TNF blockers and in 40.4% (n=42) in patients on DMARDs; p<0.0001). The presence of carotid plaques was inversely correlated with TNF blockers duration (r= -0.206, p=0.024). .	TNF blockers vs DMARDs ESR: 14.23**±8.53 vs 24.11±16.66**, p<0.0001 CRP:1.98 **±1.8 vs 3.**6±3.9, p=0.007 No differences between PsA groups regarding interleukin 6 (ng/l) (p=0.07).	—
Ortolan et al. 2020 [8]	**Mean CIMT (baseline to FU1)** 0.9 ± 0.4 vs 0.7 ± 0.1; p<0.0001 at baseline. **(FU1 to FU2)** 0.9 ± 0.3 vs 0.9 ± 0.4; p:NS. **Max CIMT (baseline to FU1)**:1.1 ± 0.4 vs 0.90 ± 0.2: p< 0.0001 at baseline. **(FU1 to FU2)** 1.1 ± 0.3 vs 0.90 ± 0.2: p: ns at FU1.	No significant variation in FMD (%) values	—	**From baseline to FU1** CRP (mg) 2.91± 1.72 vs 11.25 ± 9.16; p=0.01, hs-CRP (mg/l) (1.88 ± 2.27 vs 2.85±2.86; p=0.001) and OPG (pg/ml) (1297±615 vs 1430±648; p=0.01). Significant decrease of lipid profile (mmol/l): total cholesterol (5.1±0.93 vs 5.45±1.08; p=0.01), LDL-cholesterol (3.1±0.87 vs 3.42±0.77; p=0.02) and triglycerides (1.25±0.15 vs 1.47±0.74; p<0.0001). **At FU2,** Triglycerides increased back at FU2 (1.72±0.62 vs 1.25±0.15; p<0.0001). CRP, hs-CRP, OPG, Total cholesterol, LDL-C remained stable at FU2 (p:ns). No significant difference was observed in HDL-C levels throughout the study period.	—

Table 1. (following) Overview of eligible studies on effects of TNF inhibitors on Subclinical Atherosclerosis and Endothelial Function in Patients with Psoriatic Arthritis

First author	Primary outcomes			Secondary outcomes	
	Carotid intima media thickness	**Endothelial function**	**Carotid plaques**	**Inflammatory markers Lipid profile**	**Homeostatic and Fibrinolytic function**
Ramonda et al. [3]	**At 2 years of follow-up:** **Mean CIMT** 0.75 ± 0.12 vs 0.95 ± 0.39; P < 0.0005). **Max CIMT** and 0.90 ± 0.23 vs 1.08 ± 0.43; P < 0.0005).	**At 2 years of follow-up:** FMD (%) was unmodified: 5.3 ± 1.6 vs 5.8 ± 2.1; p:ns).	__	**At 2 years of follow-up:** Significant decrease of CRP (mg) (2.9± 1.7 vs 11.2 ± 9.2; p<0.001), OPG (pg/ml) (1219 vs 1341; p=0.011). Significant decrease of lipid profile (mmol/l): LDL-cholesterol (3.1±0.96 vs 3.1±0.87; p=0.013) and triglycerides (1.24±0.59 vs 1.47±0.82; p=0.036). No significant difference was assessed in interleukin 6 (pg/ml), VEGF (pg/ml), total cholesterol and HDL-C.	__
Deyab et al. [4]	__	At baseline: Median RHI was 2.06 (1.45-2.94). Nine patients had ED with median RHI at 1.56 (1.45-1.64). At follow-up: In PsA with ED: Median RHI were respectively 1.67 and 1.80; p:ns). RHI improved from baseline (median RHI=1.56) to 6 weeks (RHI=1.67) and further to 6 months (RHI=1.80) with no statistical significance	__	__	__

Table 1. (following) Overview of eligible studies on effects of TNF inhibitors on Subclinical Atherosclerosis and Endothelial Function in Patients with Psoriatic Arthritis

First author	Primary outcomes			Secondary outcomes	
	Carotid intima media thickness	Endothelial function	Carotid plaques	Inflammatory markers Lipid profile	Homeostatic and Fibrinolytic function
Di-Minno Et al. 2014 [5]	—	—	—	At 6 months of follow-up: 27 (35.5%) of case group achieved MDA. Both ESR and CRP decreased in case group (% Δ -percentage changes of -22% for ESR and -15% for CRP; p<0.001). Δ-percentage CRP reduction is correlated with improvements in these parameters: PAI-1 (r = 0.326, p = 0.004), PAI-1/t-PA ratio (r= 0·283, p = 0·013), and D-dimer (r = 0·250, p = 0·029).	At 6 months of follow-up: PAI-1 (p < 0.001), t-PA (p < 0.001), fibrinogen (p < 0.001), D-dimer (p < 0.001), FVIII (p < 0.001), vWF (p < 0.001), protein C p < 0.001), protein S (p < 0.001), and antithrombin (p = 0.031). No significant changes were observed in control group (p > 0.05 for all variables). TNF-α blockers significantly reduced prothrombotic markers than DMARD (e.g., Δ-percentage fibrinogen: −15.2% vs. −1.3%; p < 0.001). Among TNF-α-treated patients, those achieving MDA had greater reductions in hemostatic/ fibrinolytic variables than non-MDA patients (p < 0.05 for all). TNF-α treatment independently predicted improvements in fibrinolytic (PAI-1, t-PA) and coagulation (D-dimer, FVIII, vWF) variables (all p < 0.01).

PsA (Psoriatic Arthritis); TNF (Tumor Necrosis Factor); DMARDs (Disease-Modifying Antirheumatic Drugs); CIMT (Carotid Intima-Media Thickness); mean-max CCA (mean-maximum common carotid artery); mean-max bulb (min –maximum carotid bifurcation); ESR (Erythrocyte Sedimentation Rate); CRP (C-Reactive Protein); hs-CRP (High-Sensitivity C-Reactive Protein); OPG (Osteoprotegerin); LDL-C (Low-Density
Lipoprotein Cholesterol); HDL-C (High-Density Lipoprotein Cholesterol); FMD (Flow-Mediated Dilation); ED (Endothelial Dysfunction); RHI (Reactive Hyperemia Index); VEGF (Vascular Endothelial Growth Factor); PAI-1 (Plasminogen Activator Inhibitor-1); t-PA (Tissue Plasminogen Activator); vWF (von Willebrand Factor); FVIII (Factor VIII); and MDA (Minimal Disease Activity); FU1 (follow-up at 2 years); FU2 (follow-up at 5 years); max (maximum).

Endothelial Function

Three studies evaluated the effect of TNF-alpha inhibitors on endothelial function in patients with PsA, using either FMD or RHI as measures (8,9,11). No consistent significant improvement in endothelial function was observed. According to Deyab and al., RHI improved from baseline (median RHI=1.56) to 6 weeks (RHI=1.67) and further to 6 months (RHI=1.80) with no statistical significance (11).

Carotid Plaques

Only one study has assessed the effect of TNF-alpha inhibitors on the presence of carotid plaques in patients with PsA (7). Carotid plaques were found in 15.8% of patients treated with TNF-alpha inhibitors, compared to 40.4% in those receiving csDMARDs (p<0.0001). Atherosclerosis plaque presence was inversely correlated with the duration of TNF-alpha blocker exposure (r= -0.206, p=0.024) (7).

Effect of TNF-alpha inhibitors on atherosclerosis biomarkers

Inflammatory and Lipid Markers

Four studies evaluated inflammatory markers levels (7–10). In PsA patients treated with TNF-alpha inhibitors, both ESR and CRP showed significant reductions with delta percentage changes ranging between -22% for ESR and -15% for CRP ($p<0.001$) (7–10). Similarly, hs-CRP ($p < 0.01$) and OPG ($p=0.011$) levels decreased by the two-year mark and remained stable at five years of follow up (9). No changes were noted in IL-6 and VEGF levels (8,9). Only two studies assessed changes in lipid profiles (8,9). There was a decrease in LDL cholesterol ($p=0.013$) and in triglycerides ($p=0.036$) after two years of follow-up (Table 1).

Homeostatic and fibrinolytic markers

One study evaluated the impact of TNF-alpha inhibitors on homeostatic and fibrinolytic markers (10). After six months, patients with PsA who received TNF-alpha blockers showed significant improvement in both homeostatic and fibrinolytic markers compared to those on csDMARDs ($p<0.001$). Patients achieving minimal disease activity on TNF-alpha inhibitors had greater reductions in these markers ($p<0.005$) (10) (Table 1).

Discussion

This systematic review aimed to assess the effects of TNF-alpha inhibitors on atherosclerosis and endothelial dysfunction in PsA patients. Evaluating atherosclerosis-related measures is clinically relevant, as they provide valuable insights for predicting cardiovascular events such as stroke and myocardial infarction in this population. Overall, TNF-alpha inhibitors were found to reduce atherosclerosis progression, carotid plaque burden, and systemic inflammatory and lipid markers, although findings varied across studies. In contrast, no consistent evidence was found to support a beneficial effect of TNF-alpha inhibitors on endothelial dysfunction.

CIMT is widely recognized as a surrogate marker of subclinical atherosclerosis. Three studies evaluated the impact of TNF-alpha inhibitors on CIMT in patients with PsA (7–9). Di Minno et al. reported a significantly lower CIMT in patients receiving TNF-alpha inhibitors compared to those treated with csDMARDs, suggesting a protective vascular effect. Specifically, both mean-max CIMT values at the CCA and carotid bulb were significantly reduced in the TNF-alpha inhibitor group. Among TNF-alpha agents, adalimumab demonstrated the strongest association with reduced CIMT, followed by etanercept and infliximab (7). Moreover, a longer duration of TNF-alpha inhibitor therapy was inversely correlated with CIMT values, and treatment duration was a significant predictor of CIMT improvement in linear regression models.

These findings were first reported by Tam et al., who demonstrated that short-term TNF-alpha inhibition significantly slowed the progression of atherosclerosis in active PsA patients. Moreover, regression of maximum CIMT was observed only in those who continued long-term TNF-alpha blockers, suggesting that sustained suppression of high-grade inflammation may potentially reverse early atherosclerotic changes (19).

In contrast, findings from Ramonda et al. and Ortolan et al. did not support a regression of CIMT over time. Both studies observed a progression of CIMT after two years of follow-up, even among patients treated with TNF-alpha inhibitors (8,9). This discrepancy may be attributable to differences in study design, baseline cardiovascular risk profiles, ultrasound sensitivity, treatment adherence, or concomitant therapies. Furthermore, the possibility of irreversible vascular changes once atherosclerosis is established could limit the impact of anti-TNF-alpha therapy on CIMT progression over longer timeframes. A cross-sectional study by Eder et al. demonstrated that the proportion of patients receiving TNF-alpha inhibitors was significantly higher in the high-risk atherosclerosis category, based on ultrasound assessment, compared to those in the intermediate and low-risk groups (20). These findings highlight the need for larger, prospective studies with standardized imaging protocols and long-term follow-up to better clarify the vascular effects of TNF-alpha inhibitors in PsA.

In the study by Di Minno et al. (7), carotid plaque prevalence was significantly lower in PsA patients treated with TNF-alpha inhibitors compared to those on csDMARDs (15.8% vs 40.4%, $p<0.0001$), supporting a potential protective effect of TNF-alpha inhibition on subclinical atherosclerosis. Moreover, an inverse correlation was observed between the duration of TNF-alpha inhibitor therapy and the presence of carotid plaques ($r = –0.206$, $p = 0.024$), indicating that prolonged exposure to these agents may contribute to reduced atherosclerotic burden. These findings support the hypothesis that TNF-alpha inhibitors may slow or even prevent plaque formation by dampening chronic systemic inflammation, a key driver of endothelial dysfunction and vascular remodeling in PsA.

Nevertheless, the impact of TNF-alpha inhibitors on endothelial function in PsA remains unconclusive as current evidence does not demonstrate consistent improvement. Three studies assessed endothelial function using either FMD or RHI (8,9,11). In all these studies, no statistically significant changes were observed during follow-up. One study reported no significant variation in FMD over two years of follow-up (8). Similarly, Ramonda et al. found that FMD remained unchanged after two years of TNF-alpha inhibitor therapy ($5.3 \pm 1.6\%$ vs. $5.8 \pm 2.1\%$; p=ns) (9). In the study by Deyab et al., patients with endothelial dysfunction showed a gradual increase in RHI from baseline (median 1.56) to 6 weeks (1.67) and 6 months (1.80), but these changes were not statistically significant (11). These findings contrast with those of the systematic review by Brezinski et al., in which two out of three studies showed that TNF-alpha inhibitors improved endothelial function in patients with psoriasis and PsA (12).

The exact mechanisms underlying the potential protective effects of TNF-alpha inhibitors on endothelial dysfunction remain unclear. Patients with inflammatory arthritis (IA) have been shown to exhibit heightened

vascular inflammation compared to non-IA individuals with CVD, particularly involving increased TNF-alpha expression in the vascular media and adventitia (21,22). This deep vascular inflammation may influence the luminal compartment of the artery and alter endothelial cell phenotype, thereby contributing to endothelial dysfunction (23). Consequently, TNF-alpha inhibitors may theoretically improve endothelial function by attenuating vascular inflammation (24).

However, the observed differences in the effect of TNF-alpha inhibitors on endothelial function may, at least in part, be attributed to differences in patient populations, or other factors such as longer disease duration and treatment resistance. For instance, in the study by Deyab et al. (11), disease duration was negatively associated with changes in the RHI from baseline to 6 months, suggesting that endothelial function is more difficult to restore in patients with longstanding rheumatic disease. These findings underscore the importance of early antirheumatic intervention, not only to prevent joint destruction, but also to mitigate atherosclerotic risk. Nonetheless, larger studies are needed to confirm these observations.

Several studies included in this systematic review assessed the impact of TNF-alpha inhibitors on systemic inflammation and metabolic parameters in PsA patients. Four studies consistently reported significant reductions in inflammatory markers such as ESR and CRP (7–10). Additionally, hs-CRP and OPG levels significantly decreased by the two-year mark and remained stable at five years of follow-up, suggesting a sustained anti-inflammatory effect (9).

Although baseline OPG levels correlated with mean-CIMT, they remained slightly elevated compared to the general population at the end of the study. Given that OPG is an independent risk factor for carotid atherosclerosis progression and cardiovascular events (25,26), it may play a role in vascular remodeling in PsA (27). When combined with other biomarkers, OPG appears to be a valuable tool for monitoring vascular risk in PsA patients (28). However, no significant changes were observed in IL-6 or VEGF levels (8,9), indicating that the anti-inflammatory response may not be uniform across all cytokines and angiogenic markers.

Only two studies investigated changes in lipid profiles, showing a modest but significant decrease in LDL cholesterol and triglyceride levels after two years of treatment (8,9). In the literature, data on the behavior of metabolic biomarkers during anti-TNF-alpha treatment remain inconsistent. While some studies suggest that achieving minimal disease activity is associated with lower triglyceride levels and higher HDL cholesterol (29), others have reported increases in triglycerides and total cholesterol (30). These findings support the hypothesis that TNF-alpha inhibitors may exert favorable metabolic effects in addition to their anti-inflammatory properties, which could contribute to a reduction in cardiovascular risk.

Chronic inflammation induces a prothrombotic state by disrupting the balance between fibrinolysis and coagulation (31). The effects of TNF-alpha inhibitors on homeostatic and fibrinolytic markers in PsA patients were assessed in one study (10). After six months of treatment, those receiving TNF-alpha blockers demonstrated significant improvements in these markers compared to patients on csDMARDs ($p<0.001$). Notably, patients who achieved minimal disease activity exhibited even greater reductions ($p<0.005$), suggesting a potential link between clinical disease control and cardiovascular risk modulation.

This systematic review has several limitations that should be acknowledged. First, the number of eligible studies was relatively small. The exclusion of non-English publications may have led to the omission of relevant data. Second, most of the included studies had limited sample sizes, which may reduce the generalizability of the findings. Third, there was considerable heterogeneity across studies in terms of design, follow-up duration, types of TNF-alpha inhibitors, outcome measures, and imaging modalities, making direct comparisons and synthesis of results challenging. Third, most studies were observational, with a lack of RCTs, thereby increasing the risk of selection bias and confounding. Furthermore, not all studies accounted for traditional cardiovascular risk factors or concomitant therapies, which may have influenced the outcomes. Lastly, given the small number of studies and variability in reported results, conducting a meta-analysis was not feasible.

This systematic review highlights the potential vascular benefits of TNF-alpha inhibitors in patients with PsA. These agents may reduce subclinical atherosclerosis, as evidenced by improvements in CIMT and reduced carotid plaque burden, and consistently lower systemic inflammatory markers. However, their impact on endothelial function remains unconclusive, with inconsistent findings across studies. The favorable effects on lipid metabolism and coagulation parameters suggest a broader cardiovascular protective role. Nevertheless, the current evidence is limited by small sample sizes and methodological heterogeneity. Larger, prospective, and controlled studies are needed to better define the cardiovascular effects of TNF-alpha inhibitors in PsA, particularly regarding endothelial function and long-term cardiovascular outcomes.

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