

Biomarkers of subclinical atherosclerosis in patients with psoriatic arthritis

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Background: Psoriatic arthritis (PsA) is a chronic immune-mediated disease. It is associated with an increase in cardiovascular risk factors (obesity, hypertension, diabetes, and dyslipidemia), giving a higher risk of major adverse cardiovascular events. Patients with PsA have an increased incidence of subclinical atherosclerosis and endothelial dysfunction. The aim of this study is to perform a review of the biomarkers of subclinical atherosclerosis in patients with PsA.

Methods: A search was performed in the electronic databases (PubMed, Web of Science, Scopus, and Embase) up until July 2017. Studies were considered if they included data on biomarkers of subclinical atherosclerosis in PsA, and each article was then reviewed for quality and clinical relevance. After completing the literature search, all screened literature was summarized and discussed in our study group (CaRRDs study group).

Results: The initial search produced 532 abstracts, which were limited to 258 potentially relevant articles by preliminary review of the titles and by excluding review articles and case reports (n=274). A further 102 articles were deemed ineligible after examining the abstracts. Full texts of the remaining 156 articles were retrieved. Most articles were excluded because they were not relevant to the biomarkers of subclinical atherosclerosis in psoriasis and/or PsA. In the end, 54 articles were deemed eligible for this review.

Conclusion: Patients with PsA showed more severe atherosclerotic disease compared with patients with only psoriasis. This may have been due to the higher systemic inflammatory burden from the combination of both diseases. In patients with PsA some molecules may be considered as markers of atherosclerotic disease, and their detection may be a prognostic marker, in addition to imaging procedures, for the development of atherosclerotic disease, and could be suitable for the management of patients with PsA.

Keywords: psoriatic disease, insulin resistance, lipid profile, serum uric acid, complement C3, primary and secondary hemostasis

Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated disease. One-third of patients with skin and/or nail psoriasis will develop an inflammatory arthritis leading to severe physical limitations and disability.^{1,2} In addition to skin and joint involvement, PsA has a high prevalence of extra-articular manifestations³ and comorbidities.⁴⁻⁶ The literature reports an increased cardiovascular risk in patients with PsA.^{7,8} PsA patients show a higher prevalence of metabolic syndrome (MetS), hypertension, hyperlipidemia, obesity, and diabetes compared with those who have only psoriasis.⁴ An additional vascular risk factor is hyperhomocysteinemia, which may be determined by medications used for the treatment of PsA^{9,10} as much as by genetic and/or nutritional variations. PsA subjects may have

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increased fibrinogen, a major predictor of stroke and myocardial infarction,¹¹ and C-reactive protein (CRP) levels.¹² Moreover, a higher incidence of arterial thrombosis is related to platelet hyperreactivity, so the inflammation influences platelet reactivity and the achievement of minimal disease activity (MDA) may normalize platelet hyperreactivity, thus reducing thrombotic events.¹³

The aim of this manuscript is to perform a review on the biomarkers of subclinical atherosclerosis in patients with PsA.

Methods

A search was performed in the electronic databases (PubMed, Web of Science, Scopus, and Embase) up until July 2017. In MEDLINE, we used the search terms “psoriatic arthritis” AND “cardiovascular risk”, OR “oxidized low-density lipoproteins”, OR “nitric oxide”, OR “-nitrotyrosine”, OR “vitamin A”, OR “vitamin E”, OR “beta-carotene”, OR “homocysteine”, OR “fibrinogen”, OR “increased platelets”, OR “hypercoagulability”, OR “complement C3”, OR “C-reactive protein”, OR “uric acid”. Search limits included links to full text only, humans, English language articles, males and females, and all adult ages (Table S1). The “Related Articles” function of PubMed was used to cross-check for any additional relevant studies and the references of the reviewed articles were manually scanned for other relevant studies. Studies were included if they contained data on biomarkers of subclinical atherosclerosis in PsA, and each article was then reviewed for quality and clinical relevance. After completing the literature search, all screened literature was summarized and discussed in our study group (Cardiovascular Risk in Rheumatic Diseases [CaRRDs] study group). All literature and comments were included in the systematic review.

Results

The initial search produced 532 abstracts, which were limited to 258 potentially relevant articles by preliminary review of the titles and by excluding review articles and case reports (n=274). A further 102 articles were considered ineligible after examining the abstracts. Full texts of the remaining 156 articles were retrieved. The majority of articles were excluded because they were not relevant to the biomarkers of subclinical atherosclerosis in psoriasis and/or PsA. In the end, 54 articles were considered eligible for this review (Figure 1).

PsA and psoriasis are associated with a significantly increased risk of cardiovascular risk factors and major adverse cardiovascular events (MACEs). Ogdie et al showed a higher risk of developing MACEs in patients with PsA who were not using disease-modifying antirheumatic drugs (DMARDs) and a similar risk to that in patients with psoriasis and rheumatoid arthritis (RA).¹⁴ However, irrespective of classical cardiovascular risk factors, systematic inflammation in PsA patients plays an important role in increasing cardiovascular diseases.

A high body mass index (BMI) and obesity are both associated with an increased risk of cardiovascular mortality and morbidity.¹⁵ It has been widely demonstrated that obesity is more common in patients with psoriasis, and it is notably more common in PsA than in RA patients (28% vs 15% with BMI >27 kg/m²).¹⁶ A meta-analysis by Armstrong et al showed that there is a connection between psoriasis and obesity. In particular, psoriasis patients have 45% increased odds of being obese compared with the general population.¹⁷

Data from the literature prove that nutritional assessment in psoriatic patients may improve both the disease severity and the obesity-related comorbidities. In particular, some studies show that body weight and diet may trigger the psoriatic disease, or even exacerbate the clinical manifestations.^{18,19} PsA patients present a higher BMI than patients without joint involvement and a higher prevalence of obesity than in the general population.¹⁸ Obesity is also associated with a higher disease activity in PsA patients, but few studies have evaluated the relationship between joint disease severity and obesity in PsA patients. Similarly, in patients without joint involvement, the severity of the skin disease has been associated with BMI,²⁰ and the prevalence of obesity is higher in those with severe compared with mild psoriasis, with an OR of 1.47 (95% CI 1.32–1.63).²¹ Di Minno et al showed, in a prospective study, that increased BMI predicted lower response to tumor necrosis factor- α (TNF- α) blockers in PsA patients.²² In this study, it was also reported that weight reduction was linked with greater response to treatment with TNF- α blockers, probably due to the underdosing of medications, which may explain the lower response of the obese patients to the treatment.²³

The exact mechanism underlying the association between psoriatic disease and obesity is still unidentified. Obesity is considered a chronic, low-grade inflammatory condition which causes changes in levels of cytokines (TNF- α and IL-6) and “adipokines” (leptin and adiponectin).^{24–26} Adiponectin has

anti-inflammatory and insulin-sensitizing properties as it inhibits TNF- α , IL-6, and interferon- γ production; conversely, it also has proinflammatory effects. It leads monocytes and macrophages to produce proinflammatory IL-6, TNF- α , and IL-12. In addition, leptin is involved in the production of proinflammatory Th1 cytokines and in the inhibition of anti-inflammatory Th2 cytokines. Chen et al demonstrated higher leptin levels in psoriatic patients compared with healthy controls, and they considered psoriasis an independent risk factor for hyperleptinemia.²⁷ Similarly, resistin concentration was increased in patients with psoriasis and correlated with disease severity. Differently, in these patients, there is a decrement in plasma levels of cytokines with anti-inflammatory properties such as adiponectin compared with healthy controls, and this is inversely related to psoriasis severity and TNF- α level.^{28,29}

Moreover, monocytes, CD4 T lymphocytes, and most proinflammatory cytokines (TNF- α , IL-1 β , IL-6, and IL-18) involved in the pathophysiology of major arthritides³⁰⁻³² play a role in the induction and maintenance of the atherosclerotic process.³³⁻³⁵ Thus, in obese patients with PsA, there is a synergic action between the obesity-related inflammatory status and the immunity-related inflammation.^{36,37} In addition to this hypothesis, it was demonstrated that obesity represents a negative predictor of success of treatment with TNF- α blockers in patients with PsA.²²

Insulin resistance and diabetes

The relationship between diabetes and RA is interesting for its association with a well-documented increased risk of cardiovascular disease.³⁸ Whereas several studies support the relationship between insulin resistance and rheumatic diseases, there are few data about rheumatic diseases and diabetes. Han et al, in a cross-sectional comparative study through a large insurance database, documented an increased risk of diabetes in RA, ankylosing spondylitis, and PsA patients (prevalence ratios 1.4, 1.2, and 1.5, respectively).³⁹ In the Rochester Epidemiology Project, the authors described no increase in the risk of new-onset diabetes (relative risk [RR]=0.978) in RA patients, with an incidence rate of 7.9 per 1,000 person-years.⁴⁰ Salomon et al studied the incidence rate of diabetes among subjects with RA or psoriatic disease, and established a higher RR for incident diabetes among those with psoriatic disease, in comparison with healthy subjects.⁴¹ Similarly, RA patients showed a higher RR for diabetes in both sexes, however, this risk is reduced with age. The elevated adjusted HRs seen among subjects without glucocorticoid therapy imply that this risk is not primarily an adverse effect of this treatment.⁴¹

While several cross-sectional studies reported a higher prevalence of diabetes in PsA patients, fewer studies have assessed the risk of developing incident diabetes in patients with PsA.^{16,19,42-44} Diabetes and other metabolic diseases were reported to be at increased prevalence in many studies on PsA patients, with an OR of 2.18 (95% CI 1.36-3.50) of diabetes in PsA, and patients with severe psoriasis having a higher risk.⁴⁵⁻⁴⁷ Several mechanisms could explain the association between PsA and diabetes, such as patients' unhealthy lifestyles, the inflammatory cytokine setting that drives insulin resistance,⁴⁸⁻⁵⁰ and shared genetic loci for susceptibility to psoriasis and diabetes.^{51,52}

Lipid profile

The lipid profile in psoriatic patients has been studied for more than 50 years; nevertheless, there are still controversial results on this association. Many authors report reduced levels of high-density lipoprotein (HDL) and/or augmented levels of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and triglycerides (TGs).⁵³⁻⁵⁶ Other findings suggest no significant association between lipid serum levels and psoriasis.⁵⁷⁻⁶⁰ These studies are heterogeneous; they include patients with different disease durations, comorbidities (such as diabetes and obesity), and systemic treatments, factors that surely influence the lipid metabolism. Mallbris et al report a higher cholesterol concentration in VLDL and HDL in 200 patients studied at the onset of skin disease.⁶¹ Another important issue concerns the quality of HDL in psoriatic patients, which reflects their metabolic function. Mehta et al found a pro-atherogenic HDL profile in 112 psoriasis patients compared to controls.⁶²

Rheumatic diseases, such as RA and PsA, are associated with alterations in lipid metabolism.⁶³ It is widely recognized that an increase in TGs and a reduction in high-density lipoprotein-cholesterol (HDL-C) concentrations occur in acute-phase responses. These changes are accompanied by alterations in total cholesterol (TC) and LDL-cholesterol (LDL-C). The lipid levels, which are mediated by cytokines, are linked to host defense and tissue repair,⁶⁴ but a chronic inflammation can be involved in the development of cardiovascular disease.^{39,50} It has been hypothesized that apolipoproteins and lipoproteins contribute toward both acute and chronic inflammation.⁶⁵ HDL-C, in particular, plays an important anti-inflammatory role because it inhibits production of proinflammatory cytokines induced by T-cell contact.⁶⁶ In PsA, the data on

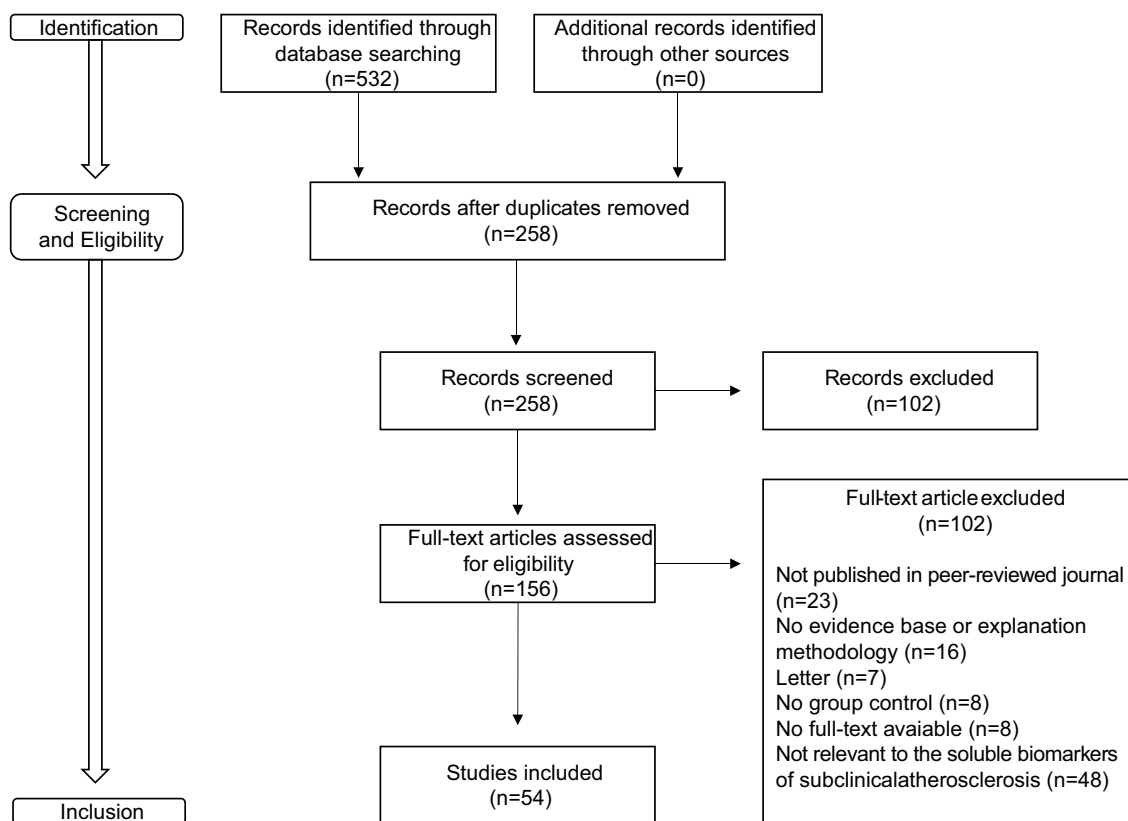


Figure 1 Flowchart of the literature review process (adapted from the PRISMA flow diagram).

serum lipid profiles are controversial. Indeed, a study examining the lipid profile in PsA patients⁶⁷ did not find a relationship between high levels of LDL-C and PsA. Nevertheless, increased levels of TC⁶⁸ and TGs^{50,69} were found to be associated with subclinical atherosclerosis in patients with PsA. Jones et al, in a study on serum lipid profile in 50 PsA patients, found an important shift in the distribution of LDL in patients with active joint disease: there was a reduction in LDL1 and LDL2 levels and an increase in LDL3 levels.⁷⁰ They also found a significant reduction in HDL-C levels, particularly subclass HDL3, which is important as HDL3-C protects less against atherosclerosis than other HDL subclasses.⁷⁰ In relation to the control group, patients with psoriasis presented a lower ratio of TC contained in HDL2 to its total content (0.05 vs 0.08) and a lower ratio in HDL3 to its total content (0.18 vs 0.25). These modifications were not linked with the significant changes in the level serum of TGs. Moreover, the reduction in HDL-C was not connected to significant changes in LDL-C in serum.⁷⁰ Significantly, Skoczynska et al also found lower levels of HDL-C and its subclasses (both HDL3 and HDL2) in PsA patients.⁷¹ The serum levels of TC and TG were normal, whereas the plasma

levels of HDL2 and HDL3 were lower than those in the control group ($p < 0.001$ and $p < 0.05$, respectively).⁷¹ More recently, Tam et al, in a case-control study, showed that patients with PsA had higher HDL-C levels, lower TC and LDL-C levels, and a lower TC/HDL-C ratio.⁵⁰ Although all these studies investigated the lipid profile in PsA patients, a possible relationship between high levels of small dense (sd)-LDL and PsA has not been demonstrated. Only the study by Jones et al looked at the presence of sd-LDL in PsA patients, but there were only 13 patients and LDL size analysis was performed by a different method (ultracentrifugation).⁷⁰ Gentile et al established that PsA patients have increased serum levels of sd-LDL independently of the presence of MetS. These findings show a possible association between PsA and the development of atherosclerosis mediated by sd-LDL. LDL size measurement can be useful both in the risk assessment for atherosclerotic disease and in identifying a subsample of high-risk PsA patients with lipoprotein alteration, who could benefit from lipid-lowering intervention.⁷² Finally, there seems to be a potential relationship between the level of inflammation and the lipid profile; indeed, dyslipidemia is more important in PsA patients with active disease.^{50,70}

Primary hemostasis (platelet aggregation)

Platelet hyperreactivity is a major predictor of arterial thrombosis and, in turn, of cardiovascular events.^{73,74} Platelets produce inflammatory mediators and mediate leukocyte incorporation into plaques through platelet-mediated leukocyte adhesion. Pathomechanisms of psoriasis imply platelet activation, mediated by chronic inflammation.^{75–78} Psoriatic patients show high titers of serum platelet-derived microparticles and P-selectin, which are both markers of platelet hyperreactivity, as reported by several studies.^{76–78}

On the other hand, several cytokines/chemokines involved in PsA, by interacting with specific platelet receptors, cause intracellular calcium mobilization, nucleotide secretion, and platelet activation.^{79,80} These data suggest a synergism between inflammation and atherothrombosis.⁸¹ However, little is known about the association of disease activity and platelet reactivity in PsA subjects. Di Minno et al evaluated platelet aggregability in 114 PsA patients by assessing the maximal light transmittance (max-A%) achieved within 5 minutes after the addition of very low concentrations of pro-aggregating agents.¹³ The authors found that max-A% values of PsA patients who achieved MDA, during treatment with TNF- α inhibitors, were comparable to those of controls and significantly lower than those of individuals with active disease. CRP values were lower in subjects with MDA than in those with active disease, and directly correlated with max-A%. Platelet hyperreactivity is a major predictor of cardiovascular events and of arterial thrombosis,⁷⁴ and these findings strongly support a synergism between inflammation and pathobiology of atherothrombosis.⁷⁸ Moreover, the study by Di Minno et al showed that platelet function is increased in patients with PsA, especially in those with poorly controlled disease.^{13,82} The correlation of CRP with max-A% and the decreasing prevalence of MDA for increasing quartiles of max-A% argue for a link between inflammation and platelet reactivity. By interacting with specific platelet receptors, cytokines/chemokines involved in PsA⁸⁰ cause intracellular calcium mobilization, nucleotide secretion, and platelet activation.⁸¹ Hyperreactivity to ADP has been reported in rheumatic diseases.⁸³ However, almost 50% of patients in that sample were receiving NSAIDs⁸⁴ and only 17% had PsA. Platelet hyperreactivity was correlated with an elevated incidence of arterial thrombosis,^{73,74} and the effect of antiplatelet agents in the vascular risk profile of subjects with PsA requires investigation.⁸³ These data suggest that

inflammation influences platelet reactivity and that achievement of MDA may normalize platelet hyperreactivity.

Secondary hemostasis (coagulation and fibrinolysis)

Novel evidence suggests an important role for changes in hemostatic system parameters in determining the cardiovascular risk in patients with RA.^{84,85} In addition to primary hemostasis (platelet reactivity), changes in fibrinolytic (tissue plasminogen activator [t-PA] and plasminogen activator inhibitor-1 [PAI-1]) and secondary hemostasis variables (coagulation proteins and natural anticoagulants) play a relevant role in the cardiovascular disease risk. Impaired fibrinolysis and/or raised levels of coagulation factors and/or reduced levels of natural anticoagulants (protein C, protein S, and antithrombin) have been recognized as major determinants of both arterial and venous thrombosis.⁸⁶ Marongiu et al described increased plasma levels of prothrombin fragment 1+2, thrombin-antithrombin complexes, and D-dimer in a cohort of 48 psoriatic patients, indicating a pro-coagulant state.⁸⁷

By enhancing platelet reactivity and affecting a series of coagulation and fibrinolytic variables, proinflammatory cytokines (ie, TNF- α and IL-6) may trigger the thrombotic risk in rheumatic patients.^{13,88} In a prospective study, Di Minno et al evaluated the changes in hemostatic and fibrinolytic variables in PsA patients starting treatment with TNF- α inhibitors.⁸⁹ They also compared changes in these variables with those found in subjects who had achieved MDA with traditional DMARDs and were on continuous treatment with such drugs. The analysis of the data on patients receiving a 6-month treatment showed that, with the exception of antithrombin, all the other hemostatic and fibrinolytic variables changed significantly.⁸⁹ In addition, the reduction in protein S, one of the major natural anticoagulants, is likely to mirror the progressive reduction in the hypercoagulable state due to treatment with TNF- α inhibitors. Moreover, the results of this prospective study provide further evidence about the link between inflammation and thrombotic risk. In particular, the authors documented that the control of the inflammatory process induced by treatment with TNF- α inhibitors is associated with a significant improvement in hemostatic and fibrinolytic parameters in PsA patients, most changes being documented in patients achieving MDA. These variables have been found to predict arterial and venous thrombosis, which are major complications in PsA.^{90,91} Previous studies have already shown that

the overproduction of proinflammatory cytokines (TNF- α and IL-6), besides playing a crucial role in the inflammatory process correlated with rheumatic disease activity,⁹² are also involved in the modulation of the fibrinolytic system.⁹³ The balance between plasminogen activators (eg, t-PA) and plasminogen activator inhibitors (eg, PAI-1) determines the total fibrinolytic potential of human blood. TNF- α has proved to be a strong agonist of PAI-1 expression and regulation.⁹⁴ In addition, high plasma levels of prothrombin fragment 1+2 and D-dimer (markers of thrombin activation and fibrinolysis, respectively) have been found in RA patients.⁹⁵ Thus, by inducing a procoagulant shift in the hemostatic balance, chronic inflammation contributes to fibrin generation and, in turn, thrombosis.^{96,97} Protein C and protein S are natural anticoagulant proteins that work in opposing hypercoagulable states.⁹⁸ In accordance with the association between natural anticoagulants and variables involved in hypercoagulable states, the changes we have reported in protein S levels are likely to be related to the changes that occur in PAI-1 and t-PA levels. In the study by Di Minno et al, besides the control of inflammation, TNF- α inhibitors have been found to down-regulate fibrinolytic and hemostatic parameters and to normalize platelet hyperreactivity, thus leading to a reduction in the cardiovascular risk.^{98,99} In addition, maximal changes in coagulation variables were found in patients achieving the MDA during treatment with TNF- α inhibitors.

High-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hsCRP) was suggested as a risk marker for potential cardiovascular events.¹⁰⁰ Some cytokines, such as IL-6, induce its production from the liver.¹⁰¹ A wide literature has shown that an elevated value of hsCRP, when added to traditional cardiovascular risk factors, can be used to support the hypothesis that atherosclerosis is first and foremost an inflammatory disease.^{102–104} Indeed, abdominal obesity and insulin resistance are predictors of an elevated hsCRP, and the presence of MetS correlates strongly with an elevated hsCRP level.^{100,101} Conversely, patients with fewer than two risk factors for MetS have low hsCRP levels.¹⁰⁰ Even in patients with mild or inactive PsA disease, low-grade inflammation as reflected by the hsCRP level was associated with obesity, insulin resistance, hypertension, and dyslipidemia, as reported by Tam et al.⁵⁰ In the same study, the authors showed that hsCRP was also associated with an increased thrombotic tendency, as demonstrated by the increased platelet count.⁵⁰ Moreover, no association was found between hsCRP and

patient's age, TC, LDL-C, TGs, apolipoprotein B, insulin, urate, or serum creatinine levels. The results were similar when only PsA patients were included in the analysis, except that the hsCRP level correlated inversely with TC.⁵⁰ Therefore, the hsCRP level in PsA patients would make the differences in the prevalence of most cardiovascular risk factors non-significant. This suggests that elevated hsCRP may not be a universal feature of chronic inflammation and may mistakenly predict coronary artery disease in PsA patients, indicating a need for alternative cardiovascular biomarkers in these at-risk populations.

Vitamins A, E, and C, and β -carotene

The increased production of reactive oxygen species (ROS) induced by atherosclerotic risk factors accelerates the disease progression in patients with rheumatic disease. This development is neutralized by natural antioxidants, such as vitamins C and E and carotenoids.¹⁰⁵ These antioxidants are scavengers of free radicals, which reduce the oxidative damage and protect LDL against oxidation.¹⁰⁶ Moreover, vitamins and carotenoids, by combating oxidative stress, may protect patients against the development of rheumatic diseases.¹⁰⁷ In patients with rheumatic diseases, although an inverse relationship between systemic inflammation and antioxidant blood levels has been reported in the literature, there is a lack of information about the relationship between antioxidants and accelerated atherosclerosis.^{108,109}

A clinical study by Profumo et al contributed toward clarifying the association between serum levels of natural antioxidants and atherosclerotic disease in RA and PsA patients.¹⁰⁹ The authors described that in PsA patients, there was a significantly higher level of vitamin A only in those with intima-media thickness (IMT) ≤ 1 mm, suggesting a possible protective action of vitamin A on the cardiovascular system in these patients. However, further studies are needed to confirm this hypothesis. Moreover, Profumo et al observed that β -carotene levels were significantly lower in RA and PsA patients than in healthy subjects, but they did not differ in accordance with the presence of subclinical atherosclerosis.¹⁰⁹ These results were in line with previous findings by De Pablo et al, showing that plasma levels of carotenoid were significantly lower in RA patients, having modified potential confounders such as smoking (which affects the serum concentrations of antioxidants).¹¹⁰ In addition, a reduced antioxidant concentration among RA patients results from increased metabolism of antioxidants. Profumo et al did not find any associations between antioxidant levels and

potential confounders among the clinical and serological variables of patients. An association of β -carotene levels in autoimmune disease but not with IMT values is suggested by lower concentrations of β -carotene in RA and PsA patients in comparison with healthy subjects, and by the inverse correlation between β -carotene content and the duration of RA. This finding further suggests the occurrence of a redox imbalance in this type of pathology, and could be linked to the higher levels of oxidized LDLs present in these patients. A recent report found that plasma concentrations of β -carotene can cause some oxidative modification of LDL *in vivo*.¹¹¹ In this report, the authors also demonstrated that vitamin E does not influence the occurrence of oxidized LDLs.¹¹¹

Serum uric acid

Hyperuricemia is a common characteristic of PsA patients,¹¹² and it has been associated with an increased incidence of cardiovascular disease and MACEs in the general population.^{112,113} Hyperuricemia is often associated with other classic cardiovascular risk factors. Fukui et al described a positive correlation between serum uric acid concentration and atherosclerosis through the carotid intima-media thickness (c-IMT) in men with diabetes.¹¹⁴ Moreover, it has been shown that an increased serum uric acid level represents a significant and independent risk factor for cardiovascular mortality in women,¹¹⁵ and an independent association has been found between serum uric acid concentration and c-IMT in Japanese men without MetS.¹¹⁶ In RA, there is an association between c-IMT >0.60 mm and carotid plaques, markers of subclinical atherosclerosis, and serum uric acid concentrations,¹¹⁷ and serum uric acid levels are significantly higher in RA patients with cardiovascular disease.¹¹⁸ A cross-sectional study shows that this association between serum uric acid levels and cardiovascular disease in RA patients is independent of other traditional cardiovascular risk factors.¹¹⁸ Gonzalez-Gay et al reported a significant correlation between serum uric acid concentration and subclinical atherosclerosis in PsA patients without clinically evident cardiovascular risk factors.¹¹⁹ In this study in PsA patients, there were significantly higher serum uric acid levels when c-IMT was >0.90 mm than when c-IMT was <0.60 mm. Moreover, the serum uric acid concentration had a high predictive power for the presence of severe subclinical atherosclerosis in PsA patients without clinically evident cardiovascular disease. In addition, in PsA patients with hyperuricemia, severe

subclinical atherosclerosis was found through c-IMT values >0.90 mm or the presence of carotid plaques in the ultrasonographic assessment of the common carotid artery.¹¹⁹

Complement C3

Complement C3 (C3) is widely accepted as an emerging risk factor for cardiovascular diseases.¹²⁰ Serum C3 has been demonstrated as a reliable marker of insulin resistance in different populations.^{121–122} C3 is involved in complement system activation because all the main activation pathways lead to the generation of C3 products (C3a and C3b). Thus, from an immunological perspective C3b is the main effector of the complement system, while from a metabolic perspective C3a appears to be more important.¹²³ Proinflammatory cytokines (TNF- α , IL-1, IL-6, and interferon- γ) augment the production of C3.^{124,125} In PsA patients, inflammatory cytokines may play a role in the increased production of C3 in adipose tissue, where gene expression of C3 is high.^{126–128} This could cause an increased insulin resistance which, in turn, determines fat storage; thus, inflammation and visceral obesity lead to the maintenance of elevated levels of insulin resistance. Ursini et al, in a cross-sectional study, suggested that serum C3 is associated with estimated insulin resistance in PsA patients.¹²⁵ Early evidence suggests that elevated C3 and C4 levels can be reduced by anti-TNF- α treatment.¹²⁹

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis, which occurs in PsA and in atherosclerosis.^{130,131} It is possible that the increased levels of VEGF observed in PsA patients has a balancing effect regarding the endothelial progenitor cells (EPCs). EPCs are a population of bone-marrow derived cells, which have the ability to migrate into areas of tissue ischemia and possess reparative qualities. They have been shown to be decreased in level and function in various inflammatory disorders, such as RA and inflammatory bowel disease.^{132–134} Some studies have demonstrated defects in the levels or function of EPCs among RA and inflammatory bowel disease patients, with an increased risk regarding cardiovascular morbidity and mortality.^{135–137} In view of these results, defective EPC function may play a role in the increased cardiovascular morbidity and mortality in these conditions. The levels and function of EPCs can improve in treated RA patients in association with clinical improvements.^{19,39,134,135,138} Nevertheless, Patschan et al showed that neither EPC

colonies nor percentages of circulating cells differed between controls and PsA patients.¹³⁹ Ablin et al presented equivalent data, with no significant differences in EPC levels among healthy controls, patients with psoriasis, and PsA patients.¹⁴⁰ This may be due to the possibility that the EPC system does not serve as a ubiquitous surrogate marker of higher cardiovascular risk in subjects with autoimmune-mediated inflammatory diseases.¹³⁹

Conclusion

Cardiovascular disease is the major cause of morbidity and mortality among PsA patients.^{81,141,142} PsA patients have an increased risk of MACEs, specifically myocardial infarction, stroke, and cardiovascular death. Ahlehoff et al showed that PsA is directly related to composite myocardial infarction, stroke, or cardiovascular death, with a rate ratio of 1.79 (95% CI 1.31–2.45).¹²¹ Ogidie et al, moreover, showed that PsA confers a fully adjusted composite cardiovascular risk among PsA patients.¹⁴ In addition, in PsA patients the prevalence of MetS and its components is higher in comparison to the general population and to other types of rheumatic disease.^{16,142} Boehncke et al described the evolution of atherosclerosis in psoriatic disease with the term “psoriatic march”.¹⁴³ In particular, the authors described that the chronic systemic inflammation in PsA patients leads to insulin resistance, with endothelial dysfunction and atherosclerosis. Patients with PsA were affected by more severe atherosclerotic disease compared with patients with only psoriasis, maybe because of the higher systemic inflammatory burden due to the combination of both diseases. Finally, the increase in cardiovascular risk in patients with PsA compared with both healthy populations and subjects matched for vascular risk factors highlights that systemic inflammation is an independent cardiovascular risk factor.¹⁴⁴ Indeed, this hypothesis is supported by the improvement in the cardiovascular risk profile following the control of systemic inflammation with anti-inflammatory treatments.^{145–147} Some molecules may be useful, as adjuncts to imaging procedures, as markers of atherosclerotic disease in PsA patients, and could be used for the management of PsA patients. To this end, an interaction among medical specialists, general practitioners, and educational programs is needed to achieve adequate cardiovascular preventive strategies in rheumatic patients.

Abbreviation list

PsA, psoriatic arthritis; MetS, metabolic syndrome; CRP, C-reactive protein; MDA, minimal disease activity;

MACE, major adverse cardiovascular event; DMARD, disease-modifying anti-rheumatic drug; RA, rheumatoid arthritis; BMI, body mass index; TNF, tumor necrosis factor; RR, relative risk; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low density lipoprotein; TG, triglyceride; sd, small dense; max-A%, maximal light transmittance; HDL-C, HDL-cholesterol; TC, total cholesterol; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; IMT, intima-media thickness; c-IMT, carotid intima-media thickness; C3, complement C3.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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Supplementary material

Table S1 Literature search strategy

MEDLINE and Embase	PubMed
1. psoriatic arthritis [title]	1. psoriatic arthritis [title]
2. cardiovascular risk [title]	2. cardiovascular risk [title]
3. 1 and 2	3. 1 and 2
4. oxidized low-density lipoproteins.mp	4. oxidized low-density lipoproteins.mp
5. nitric oxide.mp	5. nitric oxide.mp
6. 3-nitrotyrosine.mp	6. 3-nitrotyrosine.mp
7. vitamin A.mp	7. vitamin A.mp
8. vitamin E.mp	8. vitamin E.mp
9. Beta-carotene.mp	9. beta-carotene.mp
10. homocysteine.mp	10. homocysteine.mp
11. fibrinogen.mp	11. fibrinogen.mp
12. increased platelets.mp	12. increased platelets.mp
13. hypercoagulability.mp	13. hypercoagulability.mp
14. complement C3.mp	14. complement C3.mp
15. C-reactive protein.mp	15. C-reactive protein.mp
16. uric acid.mp	16. uric acid.mp
17. VEGF.mp	17. VEGF.mp
18. 3 and 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	18. 3 and 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. controlled randomized trial	19. controlled randomized trial
20. clinical trials	20. clinical trials
21. clinical study	21. clinical study
22. comparative study	22. comparative study
23. observational study	23. observational study
24. 18 or 19 or 20 or 21 or 22	24. 18 or 19 or 20
25. humans.sh.	25. humans.sh.

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