Reviews on Recent Clinical Trials, 2018, *13*, 199-209

REVIEW ARTICLE

Cardiovascular Risk Markers and Major Adverse Cardiovascular Events in Psoriatic Arthritis Patients

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Abstract: ***Background*:** Psoriatic arthritis is a chronic inflammatory arthropathy that affects 14%-30% of patients with skin and/or nail psoriasis, leading to severe physical limitations and disability. It has been included in the group of spondyloarthropathy with which it shares clinical, radiologic, and serologic features in addition to familial and genetic relationship. Beyond skin and joint involvement, psoriatic arthritis is characterized by a high prevalence of extra-articular manifestation and comorbidities, such as autoimmune, infectious and neoplastic diseases. In particular, an increased risk of cardiovascular comorbidity has been observed in psoriatic arthritis patients.

***Methods*:** A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE) up until January 2017. Studies were included if they contained data on CV disease and/or risk factors 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 (CaRDDs study group). All literature and comments were included in the systematic review.

***Results*:** The initial search produced 278 abstracts, which were narrowed to 83 potentially relevant articles by preliminary review of the titles and by excluding review articles and case report (n = 195). Thirty articles were deemed ineligible after examining the abstracts. Full texts of the remaining 53 articles were retrieved. The majority of articles excluded were due to only providing data on patients with psoriasis or due to being not relevant to the CV risk in PsA. In the end, 32 articles were deemed eligible for this review.

***Conclusion*:** Psoriatic arthritis appeared significantly associated with subclinical atherosclerosis and endothelial dysfunction and, in turn, with an increased cardiovascular risk. Thus, patients with psoriatic arthritis may benefit from a periodic assessment of surrogate markers of cardiovascular risk. This could help to establish more specific cardiovascular prevention strategies for these patients.

ARTICLE HISTORY

Received: June 29, 2017
Revised: September 27, 2017
Accepted: November 18, 2017

DOI:
10.2174/1574887113666180314105511

Keywords: Cardiovascular risk factors, endothelium dependent dilation, flow-mediated dilation, intima-media thickness, psoriatic arthritis, atherosclerosis.

1. INTRODUCTION

Psoriatic Arthritis (PsA) is a chronic inflammatory arthropathy that affects 14%-30% of patients with skin and/or nail psoriasis leading to severe physical limitations and disability [1, 2]. It has been included in the group of spondyloarthropathy (SpA) with which it shares clinical, radiologic, and serologic features in addition to familial and genetic relationship [3]. The clinical pattern of PsA is currently classified in "established PsA", which occurs in patients with evident or remittent skin and/or nail psoriasis [4], in "PsA sine psoriasis," which occurs in patients without psoriasis but with a familial history of the disease in the first or second degree relatives [5], and in "early psoriatic arthritis", consisting of an articular involvement of recent onset, occurring in subjects belonging to established or "sine psoriasis" subsets [6, 7]. Beyond skin and joint involvement, PsA is characterized by the high prevalence of extra-articular manifestation [8] and comorbidities, such as autoimmune, infectious and neoplastic diseases [9-11]. In particular, in PsA patients an increased risk of Cardiovascular (CV) comorbidity has been observed [12, 13]. In fact, PsA patients show an higher prevalence of Metabolic Syndrome (MetS) as compared with Rheumatoid Arthritis (RA) or Ankylosing Spondylitis (AS) subjects (38% *vs* 20% *vs* 11%, respectively) [14]. Similarly, an increased prevalence of hypertension, hyperlipidaemia, obesity, and type II diabetes (odds ratio ranging from 1.54 to

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1876-1038/18 $58.00+.00

2.59) has been found in PsA patients as compared with those who have psoriasis [9]. Liver steatosis, a recognized marker of them [15], is also commonly reported in PsA patients [16, 17]. As to additional VRFs, hyperhomocysteinemia may be caused by medications (methotrexate and sulfasalazine) often used in the treatment of PsA [18, 19] as much as by genetic and/or nutritional defects. Fibrinogen, a major predictor of stroke and MI [20], and CRP levels are found increased in PsA subjects [21]. Enhanced platelet reactivity in PsA patients as compared with healthy controls has also been documented [22]. Interestingly, a direct correlation between increasing quartiles of maximal platelet aggregation with inflammation (CRP levels) has been shown [23]. Growing evidence is accumulating concerning CV morbidity and mortality in PsA patients. Compared with the general population, 62% increased mortality has been reported in PsA subjects, with CV disease accounting for up to 36% of the overall mortality [24].

The aim of this review is to perform a systematic review on the CV risk in PsA patients, also investigating the potential effect of treatment.

2. METHODS

A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE) up until January 2017. In Medline, we used the search terms: 'psoriatic arthritis' AND 'cardiovascular risk', OR 'lipid profile', OR 'obesity', OR 'metabolic syndrome', OR 'hypertension', OR 'diabetes', OR 'body mass index', OR 'homocysteine', OR 'fibrinogen', OR 'increased platelets', OR 'hypercoagulability', OR 'intima-media thickness', OR 'carotid plaques' OR 'flow-mediated dilation', OR 'nitrate-mediated dilation', OR 'endothelium dependent dilation'. Similar separate searches were done with 'psoriatic arthritis' AND 'cardiovascular disease', in combination with "treatment" to ensure that no articles were missed. Search limits included links to full text only, humans, English language articles, males and females, and all adult ages. The "Related Articles" function of PubMed was used to crosscheck 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 CV disease and/or risk factors 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 (CaRDDs study group). All literature and comments were included in the systematic review.

3. RESULTS

The initial search produced 278 abstracts, which were narrowed to 83 potentially relevant articles by preliminary review of the titles and by excluding review articles and case report (n = 195). Thirty articles were deemed ineligible after examining the abstracts. Full texts of the remaining 53 articles were retrieved. The majority of articles excluded were due to only providing data on patients with psoriasis or due to being not relevant to the CV risk in PsA. In the end, 32 articles were deemed eligible for this review.

PsA is associated with a significantly increased risk of CV risk factors and major adverse cardiovascular events (MACE): myocardial infarction, stroke and cardiovascular death. In fact, the CV risk factors (obesity, hypertension, diabetes, and dyslipidaemia), contribute to an increased risk of MACE [25-27]. Ogdie *et al*, reported that the risk of developing MACE was higher in patients with PsA who were not using disease modifying antirheumatic drugs (DMARDs) and was similar to that in patients with psoriasis and RA [28]. However, irrespective of classical CV risk factors, systematic inflammation of PsA plays an important role in increasing CV diseases.

3.1. BMI and Obesity

A high Body Mass Index (BMI) and obesity have been frequently found associated with an increased risk of CV mortality and morbidity [29]. There is wide evidence 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) [14]. PsA patients tend to have higher BMI than patients without joint involvement and the prevalence of obesity in psoriatic patients is higher than in the general population [30]. Increased BMI was found in two case-control studies by Kimhi *et al.* [31] and Tam *et al.* [32]. In this study, PsA patients showed a significantly higher waist hip ratio and a significantly higher prevalence of overweight, obesity, and abdominal obesity [32]. Moreover, in some longitudinal prospective studies, obesity has been shown to be a risk factor for psoriatic disease and it predicts the development of psoriasis and PsA [33-35]. In a large population of about seventy-six thousand psoriatic patients, obesity has been associated with a high risk of incident PsA [27]. Obesity is also associated with higher disease activity in PsA patients, but few studies evaluated the relationship between the joint disease severity and obesity in PsA patients. Similarly, in psoriatic patients, the severity of psoriasis (high psoriasis area and severity index score) has been linked to BMI [36], and the prevalence of obesity is greater in those with severe compared with mild psoriasis with an OR of 1.47 (95% CI 1.32 to 1.63) [37]. Di Minno *et al*, reported that increased BMI predicted less favourable response to TNF blockers in PsA patients in a prospective study [38]. The same group also showed that weight reduction was associated with improved response to treatment with TNF blockers, probably due to the under-dosing of medications that may explain the poorer response of the obese patients to the treatment [39]. Obesity, which leads to changes in levels of cytokines (TNF, interleukin (IL)-6) and 'adipokines' (leptin, adiponectin), is associated with a low-grade chronic systemic inflammation [40-42]. On the other hand, monocytes, CD4 T lymphocytes and most proinflammatory cytokines (TNF, IL-1β, IL-6 and IL-18), that play a central role in the pathophysiology of major arthritides [43-45], are also involved in the induction and maintenance of the atherosclerotic process [46-48]. Thus, in obese patients with PsA, the obesity-related inflammatory status may acts synergistically with the immunity-related inflammation [49, 50]. Further supporting this hypothesis, obesity has been recently shown to be a negative predictor of success of a treatment with TNF blockers in patients with PsA [38].

3.2. Metabolic Syndrome

Metabolic syndrome (MetS) is a systemic proinflammatory state and, therefore, a cluster of several well-known CV risk factors that include abdominal obesity, atherogenic dyslipidaemia, hypertension, and insulin resistance [51]. There is a lack of data about the association of MetS and rheumatic disease. In particularly, there are two studies investigating the prevalence of MetS in PsA patients. Raychaudhuri *et al*, in a study on 105 patients, reported an increased prevalence (58.1%) of the MetS in PsA patients compared to the 35.2% reported from the general population [52]. Mok *et al.*, recently, on 699 RA patients, 109 with PsA and 122 with AS, reported prevalence of MetS to be 20%, 38% and 11%, respectively [14]. Taking into consideration that the MetS prevalence in their research population was between 10% and 12%, the researchers concluded that MetS prevalence is higher in patients with PsA than in both the general population and patients with RA or AS [14]. Furthermore, many studies have demonstrated a correlation between an increased MetS frequency and advancing age in patients with RA [53, 54]. In the study by Labitigan *et al.* on 1˙162 RA patients and 294 PsA patients, they found a significantly higher prevalence of MetS in PsA patients than those with RA (27% *vs* 19%, respectively), in spite of the younger age of the patients with PsA in this study [55]. In addition, in this study, a higher MetS prevalence in PsA patients was associated with higher triglyceride levels, obesity, and diabetes mellitus [55]. Instead, Özkan *et al.* in a cross-sectional study on 102 PsA patients and 102 RA patients, showed that MetS was more frequent in PsA patients than in those with RA, but obesity and diabetes mellitus did not vary in prevalence between these groups. In this study, average triglyceride levels were comparable and, the diagnosis of hypertriglyceridemia, according to NCEP-ATP III criteria, was more common in PsA patients. One of the decisive factors affecting MetS prevalence in PsA patients might be a decreased level of HDL cholesterol. The average HDL cholesterol level was 50 mg/dL in patients with PsA and 55 mg/dL in patients with RA [56]. Other studies have demonstrated a lower HDL level in patients with PsA [57, 58]. From further subgroup analysis we performed to identify factors that aggravate MetS development in patients with PsA, we conclude that factors, such as disease duration, age at disease onset, PsA type, dactylitis, enthesitis, nail involvement, and medications, do not have any effect. In the PsA group, the prevalence of MetS was significantly higher in women. MetS was also more prevalent in women in the RA control group; however, the difference was not significant. The higher prevalence of MetS in women (regardless of whether they have PsA or RA) highlights gender as an important factor in MetS development [56].

3.3. Hypertension

The prevalence of hypertension (HT) has been reported higher in PsA patients compared to the general population or to the patients with psoriasis [59, 60]. Husted *et al*, compared patients with PsA and psoriasis and documented greater HT in patients with PsA, with an estimated prevalence of 37%. This fell within the range of 25% to 49% reported in past PsA studies [9]. Han *et al.*, compared patients with RA, PsA and AS in terms of CV risk and determined a similar increased risk of HT, 1.3-fold, in all three diseases [61]. Nas *et al*, revealed a relatively increased percentage for HT in favour of RA which may be related to the high prevalence of corticosteroid usage in RA compared to patients with PsA [62]. Tam *et al*, in a case-control study on CV risk factors in PsA patients, after adjusted for BMI, recognized that PsA patients were still more likely to have HT [32]. The presence of HT has been found significantly associated with increased IMT, but the association became insignificant after adjusted for age and waist circumference [63]. The presence of HT was also found independently associated with subclinical left ventricular dysfunction in PsA patients [64]. In the PRISTINE study, significantly more patients with PsA met diagnostic criteria for elevated blood pressure than patients without PsA. The high prevalence of HT in both groups, which is consistent with rates reported in patients with psoriasis in numerous other studies [65], is troubling because this condition (like diabetes) is nearly as strong a risk factor for CV morbidity as MetS [66]. Finally, the prevalence of HT was significantly greater in PsA patients than in patients with only psoriasis, even after adjusting for conventional CV risk factors, psoriasis duration and severity, medication history (ever use of NSAIDs and/or DMARDs), and other comorbid conditions (ORs 2.08 and 2.17). This finding suggests that the additive burden of chronic inflammatory joint disease may account for the increased prevalence of HT seen in PsA compared with psoriasis without arthritis patients.

3.4. Diabetes Mellitus and Insulin Resistance

The relationship between Type 2 Diabetes Mellitus (T2D) and rheumatic diseases is interesting for its association with a well-documented increased risk of CV disease in patients with RA [67]. Although several studies support the relationship between insulin resistance and rheumatic diseases, there are, instead, few data about rheumatic diseases and T2D. Han *et al*, in a cross-sectional comparative study using a large insurance database, found an increased risk of T2D in RA, AS and PsA patients (prevalence ratio 1.4, 1.2 and 1.5, respectively) [61]. In the Rochester Epidemiology Project, the Authors found no increase in the risk of new-onset T2D (relative risk (RR) = 0.978) in RA patients, with an IR of 7.9 per 1000 person-years [68]. Recently, Salomon *et al*, studied the incidence rate of T2D among subjects with RA or psoriatic disease, and they confirm an elevated RR for incident T2D among subjects with psoriatic disease compared with non-rheumatic controls [69]. The findings among RA patients were remarkably similar elevated RR in both genders but decreasing risk with age. The elevated adjusted HRs seen among subjects not using oral or topical glucocorticoids suggests that this risk is not primarily an adverse effect of such treatments [69]. Furthermore, in psoriatic patients with severe skin disease some Authors found an increased risk of developing T2D compared with the general population [70, 71]. While several cross-sectional studies reported higher prevalence of T2D in PsA patients, fewer studies assessed the risk of developing incident T2D in patients with PsA [14, 26, 31, 72, 73]. T2D and other metabolic disease 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 T2D in PsA, and patients with severe psoriasis having a higher risk

[55, 74, 75]. Among diabetic patients, psoriasis is generally associated with higher rates of microvascular and macrovascular complications [76]. Several mechanisms could explain the association between PsA and T2D, such as patients unhealthy lifestyle [32], the inflammatory cytokine setting that drives insulin resistance [77, 78], as well as shared genetic loci for susceptibility to psoriasis and T2D [79, 80]. Finally, psoriatic patients showed signs of insulin resistance. Insulin resistance (*i.e*., reduced uptake of glucose by metabolically active cells upon exposure to insulin) is reflected at the clinical level by the so-called Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) or a pathologic oral glucose tolerance test. Using these methods, two cross-sectional studies showed that psoriatic patients exhibit insulin resistance at clinical levels [81, 82]. Some evidence exists that insulin resistance may also be a feature of PsA [83].

3.5. Lipid Profile

Rheumatic diseases, such as RA and PsA, are associated with alterations in lipid metabolism [84]. It is widely recognized that acute-phase responses lead to higher serum triglyceride (TG) and lower HDL-Cholesterol (HDL-C) concentrations. Alterations in Total Cholesterol (TC) and LDL-cholesterol (LDL-C) also seem to occur. The lipid levels, which are mediated by cytokines, are linked to host defense and tissue repair [85], but when inflammation becomes chronic, these alterations play an important role in the development of CV disease [32, 61]. It has been hypothesized that apolipoproteins (apo) and lipoproteins contribute to modulating both acute and chronic inflammation [86]. HDL-C, in particular, has an anti-inflammatory effect by inhibiting production of pro-inflammatory cytokines induced by T cell contact [87]. In PsA, the data on serum lipid profiles, are quite controversial. Although some studies examined the lipid profile in PsA patients [88], no data are currently available on a possible relationship of high levels of LDL-C with PsA. Nevertheless, an increased levels of TC [89] and TG [32, 90] were found associated with subclinical atherosclerosis in patients with PsA. Jones *et al*, in a study on serum lipid profile in 50 PsA patients, found that patients with active joint disease had a significant shift in distribution of LDL with reduced LDL1 and LDL2 levels and increased LDL3 levels [57]. They also found significantly reduced levels of HDL-C, particularly subclass HDL3, which is important as HDL3-C protects less against atherosclerosis than other HDL subclass [57]. In relation to the control group, individuals with psoriasis revealed a lower ratio of TC contained in HDL2 to its total content (0.05 *vs* 0.08) and lower ratio in HDL3 to its total content (0.18 *vs* 0.25). The decrease of plasma HDL2 and HDL3 was not connected with the significant changes in the level serum of TG, neither was the reduction of HDL-C connected with significant changes in LDL-C in serum [57]. Significantly lower levels of HDL-C and its subclass (both HDL3 and HDL2) were also found by Skoczynska *et al.* in PsA patients [58]. The serum levels of TC and TG were normal, whereas the plasma level of HDL2 and HDL3 was lower than that in the control group ($p<0.001$ and $p<0.05$, respectively) [58]. More recently, Tam *et al.*, in a case control study, found that patients with PsA had higher HDL-C levels, lower TC and LDL-C levels, and a lower TC/HDL-C ratio [32]. Although all these studies examined the lipid profile in PsA patients, no data are currently available on a possible relationship of high levels of small dense (sd)-LDL with PsA. Only the study by Jones *et al.* was conducted to investigate the presence of sd-LDL in PsA patients but LDL size analysis was performed by a different method (ultracentrifugation) and the sample size was only of 13 patients [57]. Recently, Gentile *et al.* established that PsA patients have an increased serum level of sd-LDL independently of the presence of Mets. This data suggests a possible link between PsA and the development of atherosclerosis mediated by sd-LDL. LDL size measurement gives potentially useful information in the risk assessment for atherosclerotic disease in these patients and could be useful in identifying a subsample of high-risk patients, with prominent lipoprotein abnormality, among those with the PsA diagnosis, deserving lipid-lowering intervention [91]. Finally, dyslipidaemia seemed to be more prominent in PsA patients with active disease, suggesting a potential relationship between the degree of inflammation and the lipid profile [32, 57].

3.6. Primary Haemostasis (Platelet Aggregation)

Platelet hyperreactivity is a major predictor of arterial thrombosis and, in turn, of CV events [92, 93]. Platelets produce inflammatory mediators and mediate leukocyte incorporation into plaques through platelet-mediated leukocyte adhesion. 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 [94, 95]. These data suggest a synergism between inflammation and atherothrombosis [96]. However, little is known about the association of disease activity and platelet reactivity in PsA subjects. Recently, Di Minno *et al.* evaluated platelet aggregability in 114 PsA patients by assessing the maximal light transmittance (max-A%) achieved within 5 min after the addition of very low concentrations of pro-aggregating agents [22]. The Authors found that max-A% values of PsA patients who achieved Minimal Disease Activity (MDA), during treatment with TNF blockers, were comparable to controls and were significantly lower than those of individuals with active disease. Interestingly, 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 CV events and of arterial thrombosis [93] and these findings strongly support a synergism between inflammation and pathobiology of atherothrombosis [94]. Morever, the study by Di Minno *et al.* showed that platelet function is increased in patients with PsA, especially in those with poorly controlled disease [23]. 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 PsA [95] cause intracellular calcium mobilization, nucleotide secretion, and platelet activation [96]. Hyperreactivity to ADP has been reported in rheumatic diseases [97]. However, almost 50% of patients in that sample were receiving NSAID [98] and only 17% had PsA. Platelet hyperreactivity was correlated with an elevated incidence of arterial thrombosis [93, 94], and the effect of antiplatelet agents in the vascular risk profile of subjects with PsA requires investigation [97]. These data

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

3.7. Secondary Haemostasis (Coagulation and Fibrinolysis)

Novel evidence suggests an important role for changes in haemostatic system parameters in the determinism of the CV risk in rheumatic disease [99]. In addition to primary haemostasis (platelet reactivity), changes in fibrinolytic (tissue Plasminogen Activator [t-PA], Plasminogen Activator Inhibitor-1 [PAI-1]) and secondary haemostasis variables (coagulation proteins; natural anticoagulants) are known to play a relevant role in the CV risk. Impaired fibrinolysis and/or raised levels of coagulation factors and/or reduced levels of natural anticoagulants (protein C, protein S, Antithrombin) have been recognized as major determinants of both arterial and venous thrombosis [100]. By enhancing platelet reactivity and affecting a series of coagulation and fibrinolytic variables, proinflammatory cytokines (*i.e*., TNF and interleukin 6 [IL-6]) may trigger the thrombotic risk in rheumatic patients [22, 101]. Recently, Di Minno *et al.* evaluated, in prospective study, the changes in haemostatic and fibrinolytic variables in PsA patients starting a treatment with TNF blockers [102]. In addition, the Authors compared changes in these variables with those found in subjects that had achieved MDA with synthetic DMARDs and are 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 haemostatic and fibrinolytic variables significantly changed [102]. In addition, the reduction in the protein S, one of the major natural anticoagulants, is likely to mirror the progressive reduction in the hypercoagulative state determined by the treatment with TNF blockers. 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 the treatment with TNF blockers is associated with a significant improvement of haemostatic 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 [16]. Previous studies have already shown that the overproduction of proinflammatory cytokines (TNF, IL-6), besides playing a crucial role in the inflammatory process correlated with rheumatic disease activity [103], it is also involved in the modulation of the fibrinolytic system [104]. The total fibrinolytic potential of human blood is determined by the balance between plasminogen activators (*i.e*., t-PA) and plasminogen activator inhibitors (*i.e*., PAI-1). TNF has proved to be a strong agonist of PAI-1 expression and regulation [105]. In addition, high plasma levels of prothrombin fragment 1 + 2 (F1 + 2) and of D-dimer (markers of thrombin activation and of fibrinolysis, respectively) have also been found in RA patients [106]. Thus, by inducing a procoagulant shift in the haemostatic balance, chronic inflammation promotes fibrin generation and, in turn, thrombosis [107, 108]. Protein C and protein S are natural anticoagulant proteins that play a major role in opposing hypercoagulable states [109]. Consistent with the link 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 occurred in PAI-1 and t-PA levels. In the study by Di Minno *et al*, besides the control of inflammation, TNF blockers have been found to downregulate fibrinolytic as well as haemostatic parameters and to normalize platelet hyperreactivity, thus leading to a reduction in the CV risk [101, 104, 110]. In addition, maximal changes in coagulation variables were found in those achieving the MDA during the treatment with TNF blockers.

3.8. Surrogate Markers of Atherosclerosis

Surrogate markers of atherosclerosis were all unfavourable in PsA in terms of the conferred increase in CV risk [31, 89, 90, 111-113]. Post-occlusion Flow-Mediated Vasodilatation (FMD) was impaired in PsA patients without pre-existing CV risk factors when compared with healthy controls [114]. In addition, carotid intima-media thickness (IMT) appeared consistently greater in PsA [31, 89, 90, 111, 113]. Arterial stiffness, an independent predictor of CV, is also increased in PsA patients [114].

3.8.1. Carotid Intima-media Thickness (IMT)

Carotid IMT assessment is a non-invasive imaging test for subclinical atherosclerosis [115, 116] and has been widely accepted as one of the strongest predictors of major CV events (stroke, myocardial infarction, heart failure or CV death) [117, 118]. The presence of carotid plaques is considered an even more reliable predictor of CV events than IMT [119]. Thus, these surrogate markers of subclinical atherosclerosis provide important prognostic information over and above mentioned traditional CV risk factors. Some functional and ultrasonographic assessments support the evidence of an increased CV risk profile in PsA patients. In several study, a significantly higher CCA-IMT was found in PsA patients when compared to healthy controls [31, 89, 90, 111, 113]. In a cohort study, PsA patients showed a higher carotid IMT than controls (0.76 ± 0.11 *vs* 0.64 ± 0.27, $p < 0.001$) [31]. To avoid potential confounders, Gonzalez-Juanatey *et al*. studied a population of PsA subjects without established VRFs [89]. Compared with matched controls, an impaired endothelium-dependent vasodilation ($p=0.008$) and a higher IMT ($p=0.031$) were found in the PsA group [89, 120]. Consistent with data showing a correlation between inflammation and IMT [100, 121], an association between disease activity in PsA and the presence of carotid plaques has been reported [122]. Di Minno *et al*, evaluated the effects of different treatments on IMT, and performed a case-control study [111] on 224 PsA patients (120 on TNF blockers and 104 on synthetic DMARDs) that underwent a common carotid artery (CCA)-IMT ultrasound assessment. The Authors found, in PsA patients in treatment with TNF blockers, a lower IMT both at the levels of the CCA ($p = 0.034$) and the level of the carotid bifurcation ($p = 0.002$), as compared with PsA patients in treatment with synthetic DMARDs [111]. These results clearly support the hypothesis of an association between inflammation and atherosclerotic lesions. Immune-mediated inflammation seems to play a pivotal role in the pathogenesis of atherosclerosis, being involved in endotheli-

al dysfunction, plaque rupture and thrombosis [123]. These suggestions are in line with several experimental and clinical evidences, supporting the hypothesis that premature atherosclerosis may be one of the main features of PsA and that chronic inflammation plays an important role in its pathogenesis, acting independently and/or synergistically with traditional CV risk factors. In conclusion, although PsA appeared significantly associated with subclinical atherosclerosis and, in turn, with an increased CV risk, the treatment with TNF blockers seems to be associated with a carotid IMT significantly lower as compared with matched patients receiving a treatment with synthetic DMARDs.

3.8.2. Flow-mediated Dilation and Nitrate-mediated Dilation

Flow-mediated dilation (FMD) represents a non-invasive marker of endothelial function to evaluate vascular homeostasis. It reflects the effects of several mechanisms, including vessel tone regulation, cell proliferation and inflammatory responses. In fact, chronic inflammatory rheumatic diseases are usually associated with decreased endothelial nitric oxide production, vascular damage, and premature atherosclerosis. FMD represent a surrogate marker of endothelial function and, therefore, it may play a potential role in predicting early atherosclerosis in patients with rheumatic diseases [124]. Endothelial dysfunction and subclinical atherosclerosis seem to trigger this association also in the absence of evident CV disease [120]. The decreased endothelium-dependent macrovascular function, assessed with FMD, appears to be evident in early RA diagnosis, but does not appear to be further influenced by disease duration [125, 126]. Chatterjee-Adhikari *et al.* more recently, in a case-control study, confirmed the association between subclinical atherosclerosis and early RA. The Authors showed that FMD% was significantly lower in RA patients [5.26 (2.9-10.6)] as compared with controls [10.34 (7.4-14.3)] (p=0.004) [127]. Moreover, some Authors described an association between disease activity and FMD described in RA patients [126, 128, 129]. In addition, a positive correlation of FMD with rheumatoid factor was also reported by Chatterjee-Adhikari *et al.* [127] as well as with the HLADRB1*04 shared epitope [130]. In PsA, in several reports, a lower FMD was found in patients compared to controls [122, 131-133]. As in RA, also in PsA, there are concerns about the long-term response to TNF blockers on endothelial dysfunction *via* FMD assessment [134, 135].

3.8.3. Arterial Stiffness and Pulse Wave Velocity

In addition to the traditional CV risk factors, arterial stiffness has been recently recognized as an independent predictor of CV risk [136, 137], being an expression of arterial distensibility and arterial compliance and thus of the elastic properties of large and medium sized vessels [138]. Pulse wave velocity (PWV) is a measure of early structural vascular changes, which is determined by the elasticity and other properties of the artery, and is correlated with arterial distensibility and stiffness. An increase in brachial-ankle PWV by 100 cm/s corresponds to an age-, sex-, and risk factor adjusted increase of 12% in total CV events, and 13% in CV mortality, respectively [139]. Few studies have shown increased arterial stiffness and evidence of atherosclerosis in patients with classical psoriasis [140, 141]. Costa *et al.*, in a case-control study, showed that in the PsA patients, there was an increase of aortic stiffness but they failed to find a correlation between ESR or CRP and PWV in PsA patients [142]. However, this study was limited by small sample size and cross-sectional study design and was unable to assess the effect of cumulative inflammation over time. The effect of cumulative inflammatory burden in arterial stiffness in patients with RA is controversial [143, 144]. More recently, Shen *et al*, showed that PsA patients have increased arterial stiffness compared with healthy control subjects. Cumulative inflammatory burden contributes to the increased arterial stiffness independent of traditional CV risk factors, suggesting that increasing arterial stiffness may be one of the mechanisms linking inflammation and CV disease in PsA [145].

3.9. Major Adverse Cardiovascular Events

PsA patients have an increased risk of MACE, specifically myocardial infarction, stroke and CV death. In detail, PsA has linked to obesity, hypertension, diabetes and dyslipidaemia, which contribute to an increased risk of MACE [25-27]. Few earlier studies have investigated CV events in PsA patients. Juneblad *et al.*, recognized no significant difference in the number of CV events among the PsA patients irrespective of treatment with synthetic DMARD or biologic DMARD, although the use of NSAID was less common in those patients who had died and in patients with a CV events [146]. Therefore, Ahlehoff *et al.* showed that PsA is directly related to composite myocardial infarction, stroke, or CV death with a rate ratio of 1.79 (95 % CI 1.31-2.45) [147]. Another study, by Ogidie *et al*, has shown that PsA confers a fully adjusted composite CV risk among PsA patients not taking DMARD (HR 1.24;95% CI 1.03-1.49), as well as among PsA patients taking DMARD (HR 1.17; 95% CI 0.95-1.46) [28]. The Authors reported an increased incidence of MACE in PsA, psoriasis and RA. The HRs for RA and psoriasis were similar to risk estimates in previous studies providing internal validity for the study results in patients with PsA and external validity for the study as a whole [28]. The results of the study suggest the need for improved screening and management of traditional CV risk factors in patients with inflammatory diseases. While more extensive studies are necessary to refine the risks associated with PsA, these data suggest that PsA poses an independent risk of CV risk factors and MACE. Some researchers even suggest that the association of PsA with CV risk factors and MACE may be stronger than that in psoriasis [9, 90].

CONCLUSION

Overall, many literature data support the possibility of an increased CV risk in patients with rheumatic diseases. CV disease is the major cause of morbidity and mortality among PsA patients with severe psoriasis [23, 24]. Furthermore, the prevalence of MetS and its components is higher among patients with psoriatic disease compared with the general population and those with other types of articular disorders [14, 56]. 'Psoriatic march' was a term coined by Boehncke *et al.* to describe the evolution of atherosclerosis in psoriatic disease [148]. It suggests that chronic systemic inflammation that is part of severe psoriasis and PsA leads to insulin resistance, resulting in endothelial dysfunction and atheroscle-

rosis. PsA patients suffered from more severe atherosclerotic disease compared with psoriatic patients, possibly due to higher systemic inflammatory burden due to the combination of skin and joint diseases. The finding that the vascular morbidity/mortality of rheumatic patients resembles that of T2D, further helps define the severity of the CV risk in this clinical setting [149]. The increase of CV risk in patients with rheumatic diseases as compared with both healthy populations and Vascular Risk Factors (VRFs)-matched subjects support the notion that systemic inflammation acts as an independent CV risk factor [150]. The improvement of the CV risk profile following the control of systemic inflammation by anti-inflammatory treatments argues for this possibility as well [151, 152]. While this implies that the incidence of CV morbidity/mortality should be reevaluated according to an optimal inflammation control (*i.e*., achieving MDA), inflammation/disease activity has been recently suggested to be included in the CV risk factor profile of such patients [150]. However, scores currently used for the general population (*e.g*., the Framingham score; the Systematic Coronary Risk Evaluation model) [153, 154], do not take into account the role of inflammation [155]. Based on standard algorithms, the European League Against Rheumatism (EULAR) [156] suggested the application of 1.5 multiplier to the risk calculated in rheumatic patients. While appealing for its simplicity, this approach requires a long-term validation in which repeated CV risk assessments in rheumatologic settings are mandatory [156]. In spite of their inherent limitations, studies with TNF blockers suggest that while lowering systemic inflammation, these drugs are associated with the best rheumatologic and CV outcome. However, the impact on long-term CV prognosis of these patients cannot be ruled out based on available data. Moreover, due to their high costs, current guidelines suggest that TNF blockers should be used only after the failure of synthetic DMARDs treatment [157]. This argues for an urgent identification of early predictors (clinical and/or laboratory) of a poor achieving of MDA with synthetic DMARDs and, in turn, of candidates for treatments with TNF blockers. Such information will also help answer the question whether the CV risk profile should be taken into account while choosing the appropriate anti-rheumatic treatment. To this end, a tight interaction among experts (rheumatology, internal medicine, cardiology) and general practitioners and common educational programs will provide a reliable background for adequate CV preventive strategies in rheumatic patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Raffaele Scarpa, Antonio Del Puente, Rosario Peluso, Matteo Nicola Dario Di Minno have acted as paid lecturer or board member and received grants and honoraria in the last 36 months for researches unrelated to the present study. All the other authors have nothing to declare.

ACKNOWLEDGEMENTS

The authors want to thank the members of the CaRRDs (Cardiovascular Risk in Rheumatic Diseases) study group: Matteo Nicola Dario Di Minno, Roberta Lupoli, Antonella Scalera, Alessandro Di Minno, Pasquale Ambrosino, Giovanni Tarantino, Giovanni Di Minno (Department of Clinical Medicine and Surgery, Regional Reference Centre for Coagulation Disorders, Federico II University, Naples, Italy); Rosario Peluso, Raffaele Scarpa (Department of Clinical Medicine and Surgery, Rheumatology Research Unit, Psoriatic Arthritis Clinic, Federico II University, Naples, Italy); Salvatore Iervolino, Nicola Pappone (Rheumatology and Rehabilitation Research Unit "Salvatore Maugeri" Foundation, TeleseTerme (BN), Italy).

FUNDING

This study has been performed in the frame of the project entitled ‘Biomarkers of cardiovascular risk and disease activity in patients with psoriatic arthritis: modifi cations induced by treatment with TNF-alpha blockers’ [GR-2011-02352752] funded by the Italian Ministry of Health.

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