Improving cardiovascular health and metabolic comorbidities in patients with psoriatic arthritis

Numerous studies have suggested a link between psoriatic arthritis (PsA) and comorbidities, in particular cardiovascular disease and metabolic comorbidities such as diabetes. The co-existence of these comorbidities is likely the result of systemic inflammation. In order to improve the health of patients with PsA and provide optimal care, these comorbidities must be addressed. However, little is known about how to improve metabolic and cardiovascular health in patients with PsA. In this perspective, we describe the research needs in the area of improving cardiovascular disease and metabolic comorbidities among patients with PsA.

Keywords: cardiovascular disease • diabetes • metabolic disease • obesity • psoriatic arthritis • research

PsA is associated with an increased risk for metabolic comorbidities including cardiovascular disease

Several studies have now demonstrated an increased risk for metabolic comorbidities among patients with psoriasis and psoriatic arthritis [1–2]. In particular, patients with PsA have significantly increased risk of developing incident diabetes and major adverse cardiovascular events (the combined endpoint myocardial infarction, stroke and cardiovascular death) [3,4]. The prevalence of hypertension, diabetes, dyslipidemia, obesity, fatty liver disease and metabolic syndrome are increased in patients with PsA compared with controls [5]. Furthermore, in some studies, the prevalence of these disorders is higher in patients with PsA than that among patients with psoriasis without PsA [6]. Numerous studies have now reported these associations, but the solution to the problem is less clear. Little is known about how to improve cardiovascular and metabolic comorbidities in patients with PsA and how these comorbidities affect disease outcomes.

Why is it important to improve the cardiovascular & metabolic health of patients with PsA?

Cardiovascular disease and metabolic comorbidities, such as obesity and diabetes, contribute to earlier death, reduced quality of life, increased healthcare costs and more complex disease management. The US Center for Disease Control (CDC) notes that heart disease, stroke, diabetes and obesity ‘are among the most common, costly, and preventable of all health problems’ [7]. Cardiovascular disease is the most common cause of death in developed nations and the second leading cause of disability-adjusted life years (DALYs; the total number of years lost to illness, disability or premature death) [8]. Diabetes is the strongest risk factor for cardiovascular disease and has a substantial impact on quality of life and functional ability. Despite improvement in cardiovascular risk reduction and declining smoking rates, the overall prevalence of cardiovascular disease in the USA is projected to continue to rise due to increasing the incidence of obesity and diabetes [9]. Both cardiovascular disease and metabolic disorders, such as diabetes, contribute to reduced qual-
life of PsA, the greater the impact on quality of life [11]. Furthermore, the presence of these comorbidities in patients with psoriatic disease has implications for both providers and patients: selection of therapies is more complicated for rheumatologists, dermatologists and primary care providers and patients have more physician visits and medications to manage [12]. Knowing that patients with PsA are at risk for development of these comorbidities, we have the ability to prevent these negative outcomes, or at the very least, to identify these disorders early in order to improve long-term outcomes for our patients.

Managing metabolic disease: implications for psoriatic arthritis disease control

Recent studies have suggested that metabolic comorbidities have an effect on disease activity and medication effectiveness [13]. It may, therefore, be important to treat the comorbidity in order to improve outcomes related to psoriatic arthritis. DiMinno and colleagues demonstrated that hepatic steatosis, carotid plaques and obesity are negative predictors of achieving and maintaining minimal disease activity (MDA) [14,15]. Further informing this relationship, Eder et al. demonstrated a dose-response association between obesity and achieving sustained MDA [16]. DiMinno and colleagues subsequently performed a randomized study in which patients initiating a TNF-\(\alpha\) inhibitor after failure of an oral DMARD were either assigned to a ‘hypo caloric diet’ (<1500 kcal/day) or ‘self-managed diet’ (in which patients were told to limit the use of oil and to increase vegetables and fish) [17]. Regardless of the assigned diet, patients who lost at least 5% of their initial body weight had a significantly higher rate of achieving MDA (OR: 3.75 for those who lost 5–10% of their body weight and OR 6.67 for those who lost >10% of their body weight). Although the TNF-\(\alpha\) blocker dose-to-weight ratio could contribute to improved disease activity, a subgroup analysis of patients on infliximab (in whom the dose for weight was changed as weight changed) revealed the same effect. The impact of weight loss may thus extend beyond pharmacodynamic properties of these medications. These results support the proinflammatory role of cytokines and adipokines produced by adipose tissue in worsening disease activity [18].

Inflammation & cardiometabolic disease

Despite being seemingly an organ-specific inflammatory disorder, psoriatic disease is associated with systemic inflammation that is not limited to the skin or the joints. Likewise, it is now widely accepted that atherosclerosis, the main cause of cardiovascular diseases, is an inflammatory disorder in which immune mechanisms interact with atherogenic lipid particles to initiate and propagate lesions in the vascular walls [19]. The inflammatory response in atherosclerosis is regulated by both the innate and adaptive immune systems via the action of cytokines. Increased activity of autoreactive Th1 cells and reduced activity of regulatory T cells resulting in a release of proinflammatory cytokines, such as TNF-\(\alpha\) and IFN-\(\gamma\), are shared pathogenic pathways for the development of atherosclerosis, arthritis and psoriasis [20–22]. The effect of TH17 cell and IL-23/IL-17 axis on promotion and propagation of atherosclerosis is less clear [23]. Metabolic abnormalities including obesity and diabetes mellitus are also strongly linked with systemic inflammation. The adipose tissue is considered to be an endocrine organ that produces a variety of proinflammatory cytokines. These cytokines have deleterious effects on multiple organs including the induction of glucose intolerance and proatherogenic lipid profile. Psoriatic patients display abnormalities in the innate and adaptive immune system that result in high serum levels of proinflammatory cytokine that potentially play a role in the accelerated atherogenesis and metabolic abnormalities found in these patients [24,25].

The extent of inflammation, as reflected by the clinical manifestations of psoriatic disease and by soluble biomarkers, correlates with cardiovascular risk. Several observational studies reported a dose-response association between the severity of psoriasis and PsA and the occurrence of cardiovascular events [26–28]. Patients with more severe clinical manifestations of PsA, including elevated number of dactylitic digits and actively inflamed joints are at higher cardiovascular risk. In line with these findings, studies that used surrogate endpoints of atherosclerosis found an association between measures of disease activity and the extent of atherosclerosis. The assessment of functional and morphological features of the vascular wall provides important insights about the complex interaction between inflammation, cardiometabolic risk factors and atherogenesis [29]. Abnormalities in endothelial function caused by exposure to inflammatory mediators or oxidative stress occur in early stages of atherosclerosis. These abnormalities, as measured by flow-mediated endothelial dependent vasodilatation in the brachial artery, were found to be more prevalent in patients with PsA compared with controls and correlated with serum biomarkers of inflammation [30]. Recent advances in imaging studies allow direct visualization and quantification of vascular inflammation using FDG-PET/CT, which is an important component of plaque formation and rupture. Rose et al. assess vascular inflammation in 65 patients with psoriatic
disease [31]. They found that sacroiliitis was associated with an increased vascular inflammation after adjusting for traditional cardiovascular risk factors and PsA. Morphological studies of vascular wall abnormalities assess late stages of atherogenesis by estimating the extent of atherosclerotic plaque burden using ultrasound, CT or MRI of medium to large arteries. Eder et al. reported that patients with high burden of carotid atherosclerosis tended to have elevated levels of inflammatory markers (measured by ESR, leukocyte count) and active PsA (measured disease activity in PsA [DAPSA] score) during the course of their disease [32]. Interestingly, no association was observed between the duration of psoriatic disease and the extent of atherosclerosis.

Metabolic abnormalities are also linked with the extent of psoriatic disease-related inflammation. The severity of psoriasis and PsA is associated with abnormal levels of serum biomarkers that reflect metabolic abnormalities and predict future cardiovascular morbidity. Psoriasis severity correlates with insulin resistance, abnormal levels of resistin and leptin. PsA is associated with measures of insulin resistance and leptin compared with psoriasis alone [25]. These observations support the notion that cumulative high level of systemic inflammation promotes atherogenesis and metabolic abnormalities in psoriatic disease and raise the question of whether effective suppression of inflammation reduces cardiovascular risk in patients with psoriatic disease.

**Strategies for improving cardiovascular disease & metabolic comorbidities in patients with PsA**

**Improve screening for & management of traditional cardiovascular risk factors**

An obvious strategy for improving cardiovascular disease is to identify and then manage traditional cardiovascular risk factors such as obesity, smoking, hypertension and dyslipidemia. While this is a simple statement, embedded within are many complex, unanswered questions.

**Improve recognition of cardiometabolic disease**

Both physicians and patients must recognize the increased risk for cardiovascular and metabolic disease in PsA. Educational strategies aimed at patients and physicians are needed. Continuing medical education activities for physicians and pamphlets for patients are potential strategies but it is not clear that simply educating either group changes behavior. Studies are needed to identify the gaps in education and how to best deliver the information to physicians and patients. For example, qualitative research efforts to better understand barriers to screening could lead to the development of directed physician materials, medical record reminders and templates, or online teaching modules. Furthermore, improving recognition goes beyond education: patients need to be empowered to act upon knowledge, for example, to ask providers about their individual risk. Similarly, qualitative research may lead to an improved understanding of how we can best empower patients to assist in coordinating their own care. Additionally, utilization of patient action networks and support groups may stimulate patients to ask their health care providers about their cardiovascular risk.

**Assess barriers to screening for comorbidities & cardiovascular risk factors**

Assessing and deconstructing barriers to screening for cardiovascular risk factors is similarly needed. We know that CVD screening rates could be improved. This may in part be due to diffusion of responsibility: many feel cardiovascular risk stratification and assessment of comorbidities should fall to the primary care physician. Additionally, many rheumatologists may be out of touch with current screening and management practices for cardiovascular disease. Rheumatology patients are often complicated and visits are packed with assessing disease activity, managing therapy and medication side effects, and dealing with issues that are more pressing for the patient on that particular day. Similarly, dermatology visits are generally short and a visit for psoriasis can be time consuming. Understanding specific barriers and designing interventions with the help of clinical providers and patients is critical to improving screening rates [33].

**Development of quality indicators**

Another approach to improving screening and management of traditional CVD risk factors is through the use of quality indicators (QI). QIs specify either a minimum requirement or optimum standard of care and may be used for quality improvement, pay for performance or accreditation. Significant debate exists regarding the use of quality indicators, in particular as pay-for-performance measures. However, in the USA, quality indicators are a reality in the era of the Affordable Care Act. An international expert panel recently developed 11 cardiovascular quality indicators for rheumatoid arthritis (Box 1) [34]. While relevant for rheumatologists, the authors emphasized that the responsibility for these quality initiatives is shared among all of the patient’s care providers and suggest the use of these quality indicators to improve communication among providers. The investigators plan to validate the use of the QI developed in clinical prac-
Develop of guidelines for cardiovascular risk stratification in PsA

Development of guidelines specific to patients with psoriatic disease, or inflammatory disease more broadly, may improve physician recognition of increased cardiovascular risk and screening for CVD and CVD risk factors. The European Union League Against Rheumatism (EULAR) and the Canadian Dermatology-Rheumatology Comorbidity Initiative have both released recommendations for the management of cardiovascular disease and comorbidities respectively in patients with RA, psoriasis and PsA [35,36]. The American Academy of Dermatology also included information about the comorbidities in their guidelines for the treatment of psoriasis and PsA [37]. However, development of such guidelines is difficult given the relative lack of evidence to inform risk stratification among patients with these inflammatory diseases. Several studies have demonstrated that existing risk stratification tools (e.g., Framingham and SCORE) underestimate the true inflammatory burden in patients with rheumatoid arthritis, psoriatic arthritis and psoriasis [38–42]. Additional studies to determine risk factors and develop clinical prediction models for cardiovascular disease among patients with psoriatic disease are needed [43]. Questions to be answered include whether level of inflammation should be included and, if yes, how inflammatory burden should be measured. This is particularly difficult in psoriatic arthritis as the disease is highly heterogeneous. Furthermore, clinical prediction models would need to be validated and then stud-

- Communication of increased CV risk in RA: the treating rheumatologist should communicate to the primary care physician (PCP), at least once within the last 2 years, that patients with RA have an increased CV risk.
- CV risk assessment: a formal CV risk assessment according to national guidelines should be done at least once in the first 2 years after evaluation by a rheumatologist; AND if low risk, it should be repeated once every 5 years; OR if initial assessment suggests intermediate or high-risk, then treatment of risk factors according to national guidelines should be recommended.
- Smoking status and cessation counseling: smoking and tobacco use status should be documented at least once in the last year, and if they are current smokers or tobacco users they should be counseling to stop smoking.
- Screening for hypertension: blood pressure should be measured and documented in the medical record at ≥80% of clinic visits.
- Communication to PCP about a documented high blood pressure: if a patient has a blood pressure measure during a rheumatology clinic visit that is elevated (systolic blood pressure ≥140 and/or diastolic blood pressure ≥90), then the rheumatologist should recommend that it be repeated and treatment initiated or adjusted if indicated.
- Measurement of a lipid profile: a lipid profile should be done at least once in the first 2 years after evaluation by a rheumatologist. If low risk according to CV risk scores, the lipid profile should be repeated once every 5 years; OR if CV risk assessment suggests intermediate or high risk, then treatment according to national guidelines should be recommended.
- Screening for diabetes: diabetes should be screened for as part of a CV risk assessment at least once within the first 2 years of evaluation by a rheumatologist and once every 5 years in low-risk patients or yearly in intermediate-or-high-risk patients. If screening is abnormal, this information should be communicated to the primary care provider for appropriate followup and management, if indicated (more detail is provided in the original publication).
- Exercise: physical activity goals should be discussed with their rheumatologist at least once yearly.
- BMI screening and lifestyle counseling: BMI should be documented at least once every year and if the patient is overweight or obese according to national guidelines, they should be counseled to modify their lifestyle.
- Minimizing corticosteroid usage: if a patient is taking oral corticosteroids, there should be evidence of intent to taper the corticosteroids or reduce to the lowest possible dose.
- Communication about risks/benefits of anti-inflammatorries in patients at high risk of CV events: if the patient has established CV disease OR is at intermediate or high CV risk AND is taking a nonsteroidal anti-inflammatory drug (or cyclooxygenase -2 inhibitor), then a discussion about the potential CV risks should be documented.

Adapted with permission from [34].
ies to assess uptake and long term performance would be required. Ultimately, risk stratification tools should change practice and improve intermediate and/or long-term outcomes (e.g., does cardiovascular risk assessment and subsequent management improve the rate of cardiovascular disease in patients with PsA compared with the general population?) As risk stratification methods are developed, examination of the additive benefit of imaging and biomarkers in risk assessment are also needed.

**Optimize the management of cardiovascular disease & metabolic comorbidities in PsA**

**Improve adherence to recommendations for a healthier lifestyle patients with PsA**

Once physicians have assessed a patient's cardiovascular risk profile, several potential interventions now lie ahead: lifestyle changes including diet modification, increased exercise, weight loss and smoking cessation as well as prescribing of medications, whether for their skin and inflammatory arthritis or for hyperlipidemia and hypertension. These interventions may be overwhelming for both the patient and physician. Fitting successful counseling into a short follow-up visit may not be possible. Furthermore, even under the best of circumstances, patient adherence to these interventions may be suboptimal [44,45]. Therefore, improving the cardiovascular and metabolic health of our patients will necessitate the development of targeted interventions that are designed for patients who have skin and joint disease that may limit their functional ability. Studies to address adherence and effectiveness of such interventions in both the short-term and long-term are subsequently needed.

**Develop exercise recommendations for improved cardiovascular health & disease activity**

Regular exercise can significantly improve cardiovascular risk. Additionally, in rheumatoid arthritis, exercise has the added benefit of decreasing disease activity [46–48]. However, patients with inflammatory arthritis have many barriers to physical activity such as the belief that exercise will hurt their joints, lack of understanding about why physical activity is important for their health, decreased self-efficacy around physical activity, poor environment for exercise, inability to afford gym memberships, lack of insurance coverage for physical therapy or other structured exercise programs, perceived lack of time for physical activity, and lack of intrinsic and extrinsic motivators [49]. The role and benefits of exercise in PsA has been understudied [50]. Further studies are needed to examine the impact of exercise on both cardiovascular/metabolic outcomes and disease activity in PsA. Furthermore, methods for reducing barriers to exercise are similarly needed [51].

**Determine appropriate thresholds for lipid lowering therapy initiation**

Once metabolic comorbidities are identified, it is similarly important to determine whether management strategies should be the same for patients with PsA as for the general population. While patients with RA generally have altered lipid profiles (thought to be one of the reasons for increased adverse cardiovascular events), there may in fact be a paradoxical relationship between lipids and cardiovascular events in the setting of chronic inflammation, although this is debated [52]. This phenomenon is illustrated in RA patients where lipid levels rise as disease activity declines following initiation of treatment for RA [53]. Less is known about lipid levels and how they change with therapy in PsA [54]. Furthermore, it is unclear whether low density lipoprotein thresholds used for initiation of therapy in the general population should be used for patients with PsA or whether a lower cutoff value is needed. Understanding what role statins play will be important, particularly in a disease where liver abnormalities are common due to the high prevalence of fatty liver disease and the high propensity for the development of diabetes.

**Impact of treatment for comorbidities on PsA outcomes**

Identifying and managing comorbidities may lead to improvements in quality of life, disease activity and therapy response. In the previously mentioned study by DiMinno et al., weight loss resulted in an improved response to TNF-α inhibitors [17]. Similarly, statins may also have an anti-inflammatory effect and may result in improved mortality [55,56]. Is it also possible that improved control of diabetes or improved fatty liver disease leads to improved disease activity? Can dietary changes or supplements improve both metabolic disease and inflammation? Studies are needed to address these concepts.

**Determine the impact of therapy for PsA on comorbidities**

The suppression of inflammation is a promising novel approach for the management of cardiovascular risk in the general population and among patients with chronic inflammatory conditions [57]. Two ongoing clinical trials (CIRT and CANTOS) assess the efficacy of methotrexate and IL-1β blockers in cardiovascular risk reduction among high risk individuals who do not have arthritis or psoriasis [58]. The effect of DMARDs and biologics on cardiovascular outcomes in psoriatic disease has only been assessed in observational studies. A recent meta-analysis found that systemic therapy with DMARDs
or TNF-α blockers was associated with reduced risk of developing cardiovascular events (RR 0.75; 95% CI: 0.63, 0.91) [59]. Limited data exist about the effect of the distinct class of DMARDs in psoriatic patients. Chin et al. found a protective effect of methotrexate (adjusted RR 0.48; 95% CI: 0.29, 0.81) on cardiovascular risk in patients with psoriasis and PsA using national administrative database from Taiwan [60]. A recent study by Ogdie et al. reported a higher cardiovascular risk in PsA patients who were not using nonbiologic DMARDs compared with those who were using these medications (adjusted RR 1.34 vs. 0.93) suggesting a protective effect of DMARDs [3].

More information exists about cardiovascular risk and the use of biologic medications, in particular TNF-α blockers in patients with psoriatic disease. The use of TNF-α blockers was associated with an improved profile of cardiovascular biomarkers such as CRP, homocystein, Apo-A-I, Lp(a) and fibrinogen, however, the levels of Apo-B and triglycerides were increased (Sattar, Crompton et al. 2007). In addition, the use of TNF-α blockers was associated with a lower risk of developing diabetes mellitus in patients with psoriasis and RA (adjusted RR 0.62, 95% CI: 0.42, 0.91) [59,62]. Several large population-based studies found an inverse association between the use TNF-α blockers and cardiovascular events in psoriatic patients. Armstrong et al. reported a reduced risk of MI in psoriasis patients using TNF-α blockers compared with those using only topical treatment (adjusted RR 0.50; 95% CI: 0.32, 0.79) [63]. The use of TNF-α blockers and methotrexate was associated with reduced cardiovascular risk compared with topical medications and phototherapy in patients with psoriasis (RR 0.46; 95% CI: 0.22, 0.98 and 0.56; 95% CI: 0.42, 0.76, respectively) from Denmark. No association was found between treatment with IL-23/12 inhibitors and cardiovascular events [64]. In line with these results, Wu et al. reported that the risk of developing cardiovascular events was reduced in psoriasis patients who were using TNF-α blockers compared with those using other systemic therapies or phototherapy (RR 0.50; 95% CI: 0.32, 0.79) [66]. Overall, it appears that TNF-α blockers offer cardiovascular safety and possibly benefit and may be preferred over other systemic therapies in patients who are at increased cardiovascular risk, although relatively little is known.

Conclusion
Optimal care of the patient with PsA means not only treating the skin and joint disease but also identifying comorbidities and making sure that these comorbidities are appropriately addressed. Epidemiologic studies have provided significant advances in our understanding of comorbidities associated with psoriatic disease over the past 10 years. However, little is known about how to address comorbidities in order to improve outcomes and enhance care. Much work remains in understanding the complex relationship between psoriatic arthritis and cardiometabolic comorbidities.

Future perspective
Over the next 5–10 years, major goals for the field will be improved understanding of: the mechanism for increased metabolic disease in patients with psoriatic disease; the impact of systemic therapy for PsA on metabolic and/or cardiovascular disease; and the best methods for managing CVD and metabolic
comorbidities in the setting of systemic inflammatory disorders such as PsA. Now that CVD and metabolic disease are better recognized as part of the disease process, additional studies determining the effects of currently available and newer disease modifying agents are likely to follow. Ideally, clinical trials would investigate whether medications for PsA improve cardiovascular outcomes but the feasibility of such trials may be limited by the relative rarity of CV events and such trials may be unethical due to the need to treat patients with placebo for a prolonged period of time. Studies incorporating validated surrogate endpoints (biomarkers, vascular imaging) may thus be acceptable alternatives. In addition, such studies will need to address whether simply suppressing inflammation is sufficient or whether certain mechanisms or drug classes have direct effects on cardiometabolic disease.

Financial & competing interests disclosure
A Ogdie is supported by NIH K23AR063764. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

PsA is associated with an increased risk for metabolic comorbidities including cardiovascular disease

• Systemic inflammation is associated with psoriatic disease likely drives the development of atherosclerosis and insulin resistance. Additional research is needed to better understand the mechanisms.

How can we improve cardiovascular & metabolic outcomes in patients with PsA?

• Improved screening and detection may be achieved through assessing barriers to screening, developing quality indicators, and eventually defining PsA-specific cardiovascular risk stratification tools.

• The management of CVD and metabolic comorbidities can be optimized through improving adherence to healthier lifestyles among patients with PsA, better understanding lipid metabolism in the setting of systemic inflammation, defining thresholds for lipid lowering therapy initiation and understanding the impact of treatment of the comorbidities on PsA outcomes.

• We additionally need to better understand the impact of therapy for PsA on CVD outcomes and metabolic comorbidities.

References

Papers of special note have been highlighted as: • of interest


• Excellent review on the prevalence and incidence of cardiovascular and metabolic disorders in PsA.


7 Centers for Disease Control and Prevention. Chronic diseases: the leading causes of death and disability in the United States. www.cdc.gov/chronicdisease/overview


• First prospective interventional study to examine the effect of weight loss on achievement of minimal disease activity in PsA.


• Excellent review of mechanisms of inflammation in obesity and psoriatic arthritis.


• Reports the development of the quality indicators summarized in Box 1.


• EULAR guidelines for the management of cardiovascular risk in patients with RA and PsA.


• Demonstrates the inadequacy of the Framingham risk score in determining CV risk in patients with PsA and psoriasis.


• Summarized in Box 2.
Improving cardiovascular health & metabolic comorbidities in patients with psoriatic arthritis

Perspective


• Reports the new derivation of a cardiovascular risk score for rheumatoid arthritis. A similar method could be considered in deriving a risk score for psoriatic arthritis.


• Reports improved mortality rates in patients with RA who were taking a statin compared with those not prescribed a statin after propensity score matching.


