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Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions

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Abstract

Cardiometabolic comorbidities present a considerable burden for patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA). Both RA and PsA are associated with an increased risk of cardiovascular disease (CVD). PsA more often exhibits an increased risk of metabolically linked comorbidities such as obesity, insulin resistance, type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD). Although both RA and PsA are characterised by a state of chronic inflammation, the mechanisms that contribute to CVD risk in these conditions might not be identical. In RA, systemic inflammation is thought to directly contribute to CVD risk, whereas in PsA, adiposity is thought to contribute to a notable metabolic phenotype that, in turn, contributes to CVD risk. Hence, appropriate management strategies that consider the increased risk of cardiometabolic comorbidities in patients with inflammatory arthropathy are important. In RA, such strategies should focus on the prediction of CVD risk and its management through targeting chronic inflammation and traditional CVD risk factors. In PsA, management strategies should focus additionally on targeting metabolic components, including weight management, which might not only help improve disease activity in the joints, entheses and skin, but also reduce the risk of metabolic comorbidities and improve the quality of life of patients.

Introduction

Individuals with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) have an increased risk of cardiometabolic comorbidities compared with the general population^{1,2}. The strong association between RA and cardiovascular disease (CVD) has been well-studied and is likely related to the underlying state of chronic inflammation in RA and the accompanied increase in several pro-inflammatory cytokines that are also involved in the pathogenesis of atherosclerosis³.

By contrast, psoriatic disease, a term that encompasses both psoriasis and PsA, is considered a more metabolically-driven phenotype than RA and associated with moderately increased CVD risk compared with the general population¹. Emerging evidence from genetics studies suggest a causal relationship between BMI and psoriasis⁴. Furthermore, weight-loss interventions can increase the proportion of individuals with PsA achieving minimal disease activity (MDA)^{5,6}. Metabolic comorbidities including type 2 diabetes mellitus, dyslipidaemia and hypertension are more prominent in patients with PsA than in the general population, even after adjustment for BMI⁷. The presence of these comorbidities, in addition to underlying chronic inflammation, might contribute to the apparent increased CVD risk in patients with PsA.

Chronic inflammation is a major pathogenic process in PsA, RA and potentially in primary atherosclerosis. Pro-inflammatory cytokines such as TNF, IL-1 and IL-17 contribute to atherosclerotic plaque formation and stability⁸. Moreover, a number of pro-inflammatory cytokines that contribute to PsA and RA pathogenesis, including TNF and IL-6, function systemically and effect numerous extra-articular tissues including skeletal muscle, adipose tissue, the liver and the endothelium⁹. As such, mediators of articular and cutaneous inflammation could also potentially contribute to metabolic and atherosclerotic pathology and as such could drive co-morbidities.

In this Review, we focus on RA and PsA, two common inflammatory arthropathies that have a notable cardiometabolic burden; although the risk of cardiometabolic co-morbidities is also an important consideration for a number of other inflammatory arthropathies, including ankylosing spondylitis, such discussions are outside the scope of this Review. We discuss

evidence supporting the burden of CVD in patients with RA or PsA and outline the important function of underlying systemic inflammation. Furthermore, we discuss metabolic comorbidities including obesity, type 2 diabetes mellitus, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD) and hypertension that occur in RA and PsA (table 1). Finally, we briefly review the effects of anti-rheumatic therapies on cardio-metabolic comorbidities and suggest directions for future research.

Burden of CVD in RA and PsA

RA is associated with increased cardiovascular morbidity and mortality relative to the general population¹. By comparison, evidence supporting increased CVD risk in PsA is less-well established. The following section outlines available epidemiological data describing the occurrence of CVD in patients with RA or PsA, often reported as Major Adverse Cardiovascular Events (MACE; a composite measure that includes non-fatal myocardial infarction, non-fatal stroke and cardiovascular death), coronary heart disease (CHD) and cardiovascular events in different papers. Although data from observational studies cannot prove causality, these data highlight the risks associated with these conditions.

Rheumatoid arthritis

In 2012, a meta-analysis of 14 observational studies reported that individuals with RA had a 48% higher risk of incident CVD compared with the general population¹⁰. In particular, the findings suggested that those with RA had a 68% higher risk of myocardial infarction and a 41% higher risk of stroke compared with the general population. This latter finding was confirmed in a more recent meta-analysis in 2017, which reported a 69% higher risk of incident myocardial infarction in patients with RA after adjusting for age and sex¹¹. Although traditional CVD risk factors (for example, smoking, obesity, physical inactivity, hyperlipidaemia, type 2 diabetes mellitus and hypertension) were more prevalent in patients with RA (as well as other forms of arthritis including PsA), the relative risk of incident myocardial infarction remained considerable even after adjusting for at least one of these risk factors¹¹.

Increased RA disease severity is thought to be associated with greater risk of CVD, supporting the involvement of inflammation in cardiovascular risk. For example, in a large population-

based longitudinal cohort study, the patients with RA who had received DMARD therapy (a surrogate of severe disease) had a 58% higher risk of a MACE, whereas those not receiving DMARD therapy had a 39% higher risk, compared with the general population¹. Although there are limitations to this definition of disease severity, cardiovascular mortality was 43% to 66% higher in patients with RA compared with the general population, irrespective of DMARD use¹.

Several algorithms, such as the Framingham risk score¹² and the Systematic Coronary Risk Evaluation (SCORE)¹³, can be used to predict an individual's risk of cardiovascular events through the incorporation of traditional CVD risk factors including age, sex, systolic blood pressure and cholesterol levels. However, such algorithms can underestimate the risk of CVD in certain groups of individuals, including patients with RA^{14,15}. In an attempt to address this issue, the EULAR taskforce recommend the use of a 1.5 multiplication factor when estimating the risk of CVD in patients with RA using CVD risk prediction algorithms (except when using the QRISK3 prediction algorithm, which already incorporates a multiplication factor for individuals with a diagnosis of RA)¹⁶. The validity of this multiplication factor has been questioned by some^{17,18}; however, this approach remains one of the best options available for estimating the risk of CVD in patients with RA owing to the lack of validated RA-specific CVD risk prediction models. Such models will be difficult to generate given the requirement for large cohort numbers and a long length of follow-up to generate sufficient power in CVD outcome studies, including model validation studies.

Some researchers have suggested that the increased risk of CVD in RA is similar to that reported for type 2 diabetes mellitus¹⁹. However, when these two diseases were considered concurrently with full adjustment for other risk factors, during the development of the QRISK3 risk prediction algorithm, the risk of CVD was much greater for patients with type 2 diabetes mellitus than for patients with RA, with adjusted hazard ratios (HRs) of 2.91 and 1.24, respectively, for type 2 diabetes mellitus and RA in women (with similar differences in men)²⁰. Intriguingly, this adjusted HR for RA was less than in previous estimates, which might relate to the inclusion of glucocorticoid use as a separate entity. The adjusted HRs for CVD in women and men taking glucocorticoids were 1.81 (1.74-1.89) and 1.58 (1.5-1.66), respectively, emphasising the adverse cardiovascular effects of long-term steroid use. The QRISK algorithm

is perhaps one of the most comprehensive CVD risk algorithms and QRISK2 was one of the first algorithm to include RA as an independent risk factor, adding ~40-50% additional risk for patients with RA. However, notably, this excess risk was reduced to 1.24 in the later and more extensive version (QRISK3). This reduction might imply a lower excess risk than previous estimates because of the availability of earlier and better treatments for RA and/or because some of the excess risk in previous estimates was caused by steroid use.

In summary, although CVD risk remains greater in patients with RA than in the general population, particularly the risk of myocardial infarction, the degree of excess risk might be less than previously estimated. This reduced risk might be because of improved disease control, as well as general improvements in the management of CVD risk in patients with autoimmune disease.

Psoriatic arthritis

Compared with RA, data available on the risk of CVD in patients with PsA is less well established and more variable. A large cohort study of the entire adult Danish population reported a higher rate of MACEs among patients with PsA (adjusted rate ratio 1.79; 95% CI 1.31–2.45)²¹. However, in a UK population-based longitudinal cohort study of patients in primary care, the risk of MACEs in patients with PsA was only moderately increased compared with the general population (adjusted HR of 1.24; 95% CI 1.03 to 1.49 for patients with PsA not receiving DMARD therapy)¹. In analyses of individual MACE components, PsA was associated with an increased risk of myocardial infarction^{1,22}. However, whether PsA is also associated with an increased risk of stroke is inconsistent across different studies. Several studies have reported no statistically significant association between PsA and risk of stroke^{23,24}, whereas another study reported a 33% higher risk of stroke in patients with PsA not receiving DMARD therapy¹ and a meta-analysis suggested an overall 22% higher risk of stroke in patients with PsA²².

Traditional cardiovascular risk factors contribute to overall CVD risk in PsA. For example, in one analysis of 1091 patients with PsA and a >35 year follow-up, hypertension (relative risk 1.81; $P=0.015$) and type 2 diabetes mellitus (relative risk 2.72; $P<0.001$) were independent predictors of major cardiovascular events (defined as a composite of myocardial infarction, ischaemic stroke, revascularisation, or cardiovascular death)²⁵. The extent of disease activity

and systemic inflammation (in women) were also independent predictors. In a subsequent study of patients with either psoriasis or PsA, almost 88% of the patients had at least one modifiable cardiovascular risk factor: 17% were current smokers, 13% had type 2 diabetes mellitus, 45% had hypertension, almost 50% had dyslipidaemia and >75% were overweight or obese²⁶. Notably, a lapse in time between the diagnosis and treatment of co-morbidities in patients with PsA was also identified, with 59% of patients with hypertension and almost 66% of patients with dyslipidemia undertreated for these conditions. Such gaps between diagnosis and treatment of CVD risk factors have also been reported in RA²⁷.

In the Nord-Trøndelag Health Study (HUNT study), although the prevalence of CVD risk factors (including hypertension and obesity) were higher in patients with PsA than in the general population²⁴, this increased prevalence did not translate into a higher 10-year risk of a fatal cardiovascular event, as estimated by the risk prediction algorithm SCORE²⁴. Furthermore, in a separate analysis of the UK population, CVD mortality in patients with PsA was no different to that in the general population (adjusted HR of 1.07; 95% CI 0.79 to 1.44), although notably the confidence interval was wide¹.

Overall, although the prevalence of traditional CVD risk factors and the risk of myocardial infarction seem to be higher in patients with PsA than in the general population, whether these patients also have an increased risk of stroke is unclear. Conflicting results might in part relate to the small number of events recorded in some studies (and therefore an insufficient power to detect significant differences) or a weak association between PsA and stroke. The apparent discrepancy between risk of CVD events and risk of cardiovascular mortality in PsA is also intriguing, but might again be caused by underpowered findings.

Inflammation and risk of CVD

Inflammation has an important function in atherosclerotic plaque formation. An increased serum concentration of C-reactive protein (CRP) is associated with an increased risk of CVD in the general population²⁸, suggestive of a potential link between low grade inflammation and risk of CVD. The heightened inflammatory state in RA and to a lesser extent in PsA might contribute to an increased risk of CVD in these conditions. Hence, targeting inflammation might reduce risk of CVD in these patients.

CRP and CVD

As plasma concentrations of the acute phase reactant CRP might predict future risk of CVD²⁹, several clinical trials have investigated the effect of reducing inflammation, as assessed by reductions in CRP concentration, on CVD outcomes, both in the general population and in individuals with pre-existing CVD. For example, the JUPITER (Justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin) trial sought to ascertain whether individuals with increased CRP serum concentrations but without hyperlipidemia could benefit from statin treatment³⁰. In this study, treatment with rosuvastatin reduced both CRP concentrations and the incidence of MACEs, leading the investigators to suggest that these findings support the hypothesis that lowering CRP concentrations also lowers the risk of CVD (known as the 'inflammatory hypothesis'). However, the concentrations of low-density lipoprotein cholesterol (LDL-C) were also reduced with statin treatment, and other research suggests a near perfect linear link between LDL-cholesterol reduction and the cardiovascular benefits of statins³¹. Furthermore, in another primary prevention trial of statin treatment, once changes in LDL-C levels were accounted for, there was no link between statin-induced changes in CRP and cardiovascular benefits³². Hence, data from the JUPITER trial cannot be used to support the inflammatory hypothesis.

Since the JUPITER trial, two landmark trials assessing the inflammatory hypothesis of atherothrombosis have been published, with mixed results. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) was the first randomized controlled proof-of-concept trial to show that directly reducing inflammation, through treatment with a monoclonal antibody against IL-1 β (canakinumab; 150mg every 3 months), reduced the incidence of recurrent vascular events (HR 0.85; 95% CI 0.74 to 0.98; $P = 0.021$) independent of lipid-level lowering capacity³³. However, in the related Cardiovascular Inflammation Reduction Trial (CIRT), treatment with low-dose methotrexate to reduce inflammation did not result in any significant difference from placebo in reducing CVD events in individuals with a previous myocardial infarction or multi-vessel coronary disease and who also had either type 2 diabetes mellitus or metabolic syndrome (HR 0.96; 95% CI 0.79–1.16)³⁴. The investigators argued that this discrepancy might be explained by the failure of methotrexate to lower concentrations of CRP, IL-1 β , or IL-6; furthermore, median concentrations of CRP were also

much lower at baseline in CIRT than in CANTOS, such that those enrolled in CANTOS had higher levels of residual inflammation and might therefore have been more likely to benefit from treatment. Nevertheless, the results in CANTOS are the first to confirm the cardiovascular benefits of directly targeting inflammatory pathways. However, the benefit-to-risk ratio and cost-effectiveness of canakinumab is not sufficient enough for this treatment to be considered in routine clinical practice for secondary prevention of CVD.

RA, inflammation and atherosclerosis

RA and atherosclerosis share similar underlying inflammatory pathways, including T-cell and mast cell activation, pro-inflammatory cytokine production and increased expression of leukocyte adhesion molecules³⁵. Immune complexes and pro-inflammatory cytokines including TNF, IL-1 β and IL-6 arise primarily from inflamed target tissues including the synovium, but also potentially arise from secondary lymphoid tissues such as the spleen, lymph nodes and adipose tissue. These pro-inflammatory mediators are released into the systemic circulation and have potential effects on numerous distal tissues including the skeletal muscle, adipose tissue (with reciprocal auto-inflammatory effects), the liver and blood vessel endothelium, which can result in cardiovascular risk factor modulation including vascular dysfunction, a compositionally and quantitatively altered lipid profile, prothrombotic effects and a putative increase in insulin resistance. Such effects could promote atherogenesis (Figure 1)^{9,36}.

Numerous studies have reported an association between RA and atherosclerotic burden, with patients with RA having an increased carotid intima-media thickness and carotid plaque burden compared with age-matched and sex-matched individuals without a history of CVD³⁷. Furthermore, coronary plaques were more prevalent in patients with RA (71%) than age-matched and sex-matched individuals without an autoimmune disease (45%), as was multi-vessel disease³⁸. Notably, in patients with RA, a higher disease activity was associated with a higher risk of non-calcified and mixed plaques (composed of both calcified and non-calcified components), which seem more vulnerable and prone to rupture than fully calcified plaques^{38,39}.

Imaging using combined PET and CT scanners and the tracer fluorodeoxyglucose (FDG-PET/CT imaging) can be used to directly visualise arterial wall inflammation and measure

atherosclerotic plaque activity⁴⁰. In a small study that compared 17 patients with RA with 34 patients with stable cardiovascular disease, the patients with RA had a higher aortic uptake of FDG, reflecting higher vascular wall inflammation, which was lowered with anti-TNF therapy⁴¹. In a larger study of 91 patients with RA, aortic inflammation (assessed by FDG-PET/CT imaging) in RA was associated with a higher BMI, hypertension and the presence of rheumatoid nodules; surprisingly, aortic inflammation negatively correlated with anti-CCP antibody positivity⁴². However, this study was cross-sectional and observational in design meaning that causality could not be assessed. Nevertheless, increasing evidence supports the association between RA and the presence of more (perhaps unstable) coronary plaques³⁸.

The current evidence base linking RA to atherosclerosis mostly come from small studies and should be interpreted with caution owing to publication bias (that is, a skewing of the literature towards studies with positive results, which are more easily published than negative results). Future work should include larger studies that adjust for existing cardiovascular risk factors and include a fuller representation of the range of RA including differing severities, treatment states and disease duration. These studies are important in the modern era given the improvements in disease outcomes in patients over the years, potentially because of better management of systemic inflammation.

PsA, inflammation and atherosclerosis

Several cytokines implicated in psoriatic disease might contribute to atherosclerosis through shared chronic inflammatory pathways, including T helper 1 (T_H1) and T_H17 cell activation, pro-inflammatory cytokine release and local and systemic adhesion molecule expression. For example, the concentration of T_H1-associated cytokines (TNF, IFN γ and IL-2) and T_H17-associated cytokines (IL-17A, IL-17F, IL-22, IL-26 and TNF) is increased in the circulation and lesional skin of individuals with psoriasis or PsA compared with individuals without these conditions⁴³. These pro-inflammatory cytokines might have effects on distant organs including adipose tissue, the liver, skeletal muscle and endothelium, leading to chronic systemic inflammation and a pro-atherogenic profile (figure 1).

In particular, circulating levels of TNF, either alone or in combination with IL-17, have been associated with endothelial dysfunction⁸. Several adhesion and pro-inflammatory molecules

associated with CVD are produced by monocytes after exposure to IL-17⁴⁴. Indeed, IL-17-driven inflammation is a potential immunological link between psoriatic disease and increased CVD risk⁴⁴. Similar to in patients with RA, high levels of IL-6 in patients with PsA could promote synovitis and bone erosion⁴⁵. Finally, in agreement with a potential function of IL-6 in CVD, some polymorphisms in the gene encoding IL-6 are associated with CVD outcomes^{46,47}.

To explain the link between systemic inflammation and CVD in PsA, investigators have proposed the concept of the 'psoriatic march' whereby systemic inflammation in psoriasis causes insulin resistance, which then leads to endothelial dysfunction, atherosclerosis and eventual CVD⁴⁸. A similar pathway possibly also occurs in RA. Obesity might contribute to a state of chronic inflammation in PsA through the release of adipokines, including leptin and a variety of pro-inflammatory cytokines (such as IL-6 and TNF), from adipose tissue⁴⁸. Although this idea is interesting, on the population level, obesity is thought to contribute to CVD risk mainly via affecting lipid concentrations, blood pressure and the occurrence of type 2 diabetes mellitus⁴⁹.

Several small studies have reported an association between PsA and subclinical atherosclerosis. Flow-mediated dilatation, a potential marker of endothelial function, was impaired in patients with PsA compared with age-matched and sex-matched individuals without PsA, and carotid artery intima-media thickness was also greater in patients with PsA than in controls^{50,51}. In 2018, one study assessed the relationship between PsA, metabolic syndrome and coronary plaque burden using coronary computed tomography angiography⁵². Coronary plaques were present in 76% of patients with PsA compared with 44% of age-matched and sex-matched individuals without PsA, with greater total plaque volume and higher prevalence of mixed plaques in PsA. This latter finding is clinically relevant as mixed plaques contain a thin cap fibroatheroma, which is associated with myocardial ischaemia and a poorer prognosis⁵³. Furthermore, the presence of metabolic syndrome in PsA was not associated with quantitative measure of plaque burden (including segment involvement score, segment stenosis score, total plaque volume) and plaque composition, whereas markers of PsA disease severity, including maximum tender joint count, ESR, and CRP concentration, were associated with plaque burden (segment involvement score and

segment stenosis score). However, caution is advised in interpreting these findings as the study sample size was small (25 patients with PsA and metabolic syndrome and 25 patients with PsA without metabolic syndrome) and had a cross-sectional design. A combination of traditional risk factors and disease activity probably contribute to an increased CVD burden in PsA.

Metabolic co-morbidities in RA and PsA

Metabolic comorbidities represent a considerable burden in PsA, and, perhaps to a lesser degree, in RA (Figure 2). These comorbidities include dyslipidaemia (pathogenic changes in lipid levels), obesity, impaired glucose tolerance and subsequent type2 diabetes mellitus, NAFLD and hypertension. Many studies exploring the association between RA or PsA and comorbidities are largely observational in design and therefore residual confounding and reverse causality cannot be fully excluded.

Dyslipidaemia

In the general population, a classic dyslipidaemic profile, consisting of abnormally high serum concentrations of total cholesterol and LDL-C, as well as serum triglycerides, and abnormally low serum concentrations of high-density lipoprotein cholesterol (HDL-C), is firmly associated with an increased risk of coronary heart disease (CHD)⁵⁴. Indeed, a 1mmol/L reduction in LDL-C with statin therapy is associated with a ~20% reduction in MACEs⁵⁵, with more intensive reductions in LDL-C resulting in further reductions in risk of CVD, even in individuals who had low serum concentrations of LDL-C before treatment⁵⁶.

However, in some patients with RA, a 'lipid paradox' exists in which active disease seems to be associated with lower serum concentrations of total cholesterol and LDL-C, despite RA being an independent risk factor of CVD⁵⁷. Similar changes in total cholesterol and LDL-C also occur in patients with active PsA, but these patients also have additional features indicative of metabolic disturbances, such as obesity or insulin resistance, low concentrations of HDL-C and high concentrations of triglycerides⁵⁸.

Rheumatoid arthritis

The mechanism by which systemic inflammation in RA leads to lipid alterations is incompletely understood. One hypothesis is that the inflammatory response in active RA

leads to activation of the mononuclear phagocyte system that 'scavenges' LDL particles, hence lowering serum LDL-C concentrations.

Supporting this hypothesis, treatment to reduce inflammation in general leads to a rise in serum LDL-C concentrations⁵⁹; in particular, treatment with the IL-6 receptor antagonist tocilizumab is associated with notable increases in total cholesterol, LDL-C and triglyceride concentrations⁶⁰. The reasons for this finding seem to be linked to a reversal of IL-6-induced LDL-C clearance from the circulation⁶¹. Similar patterns of lipid changes have been observed across the studies of JAK inhibitors, which inhibit signalling downstream of IL-6^{57,62,63}. For example, treatment of patients with RA with tofacitinib, a JAK inhibitor, results in reduced clearance of LDL-C particles from the circulation and an increase in circulating cholesterol concentrations⁶⁴.

Aside from quantitative changes in some lipid particles, inflammation is also associated with changes in the composition of lipid particles and although a lot of research has been done in this area, the implications of these changes remain uncertain^{65,66}.

Psoriatic arthritis

Total cholesterol, HDL-C and LDL-C levels are often lower and triglyceride levels higher in patients with PsA relative to those without PsA². For example, one study reported that patients with active PsA had lower mean total cholesterol concentrations than age-matched and sex-matched individuals from the local population ((4.99mmol/L versus 6.08mmol/L, respectively), as well as lower mean LDL-C concentrations (3.3 mmol/L versus 4.12mmol/L, respectively) and HDL-C concentrations (1.12mmol/L versus 1.29mmol/L, respectively)⁶⁷. Such findings were also observed in another study, with patients with PsA having lower total cholesterol and LDL-C concentrations⁶⁸. A reduction in cholesterol and LDL-C concentrations is in keeping with active inflammation, but notably, the pattern of reduced HDL-C and increased triglyceride concentrations is more prevalent in patients with PsA than in patients with RA⁵⁸. As this profile is often associated with obesity and type 2 diabetes mellitus, this finding is in keeping with PsA having a more metabolic phenotype than RA.

Adiposity

Increased adiposity is associated with CVD mortality and morbidity, which is thought to be caused largely via the effect of obesity on lipids, blood pressure and diabetes risk. For every 5-unit increase in BMI in individuals with a BMI >25kg/m², the risk of dying from CVD increases by 49%⁶⁹. Obesity is strongly associated with increased risk of metabolic comorbidities, which occur more commonly in psoriasis and PsA than in RA and include hypertension, type 2 diabetes mellitus, dyslipidaemia and NAFLD. Notably, central adiposity, as assessed by waist circumference, is potentially a better marker of future risk of type 2 diabetes, especially in women⁷⁰, and is also more linearly associated with risk of incident CVD, than BMI⁷¹.

Rheumatoid arthritis

Evidence supporting a contribution of adiposity to RA pathology is mixed. In a small case-control study that compared 165 individuals with RA from the Norfolk Arthritis Register with age-matched and sex-matched healthy individuals, obesity (a BMI >30kg/m²) was associated with a three-fold higher risk of RA⁷². However, a later larger study of the UK General Practice Research Database (GPRD) that compared 579 individuals with incident RA with 4,234 age-matched and sex-matched individuals without RA found no association between obesity and risk of RA⁷³. More recent findings from a large population-based cohort study that analysed data from >500,000 individuals (the UK Biobank) suggest that an increased waist circumference is associated with greater odds of RA even after adjustment for BMI⁷⁴.

Unlike in the general population, patients with RA who are overweight (BMI 25.0–29.9 kg/m²) or obese (BMI >30.0 kg/m²) have a lower relative risk of all-cause and CVD mortality than patients with a normal BMI (18.5–24.9 kg/m²), a phenomenon known as the ‘obesity paradox’⁷⁵. Being underweight (BMI <18.5 kg/m²) is also associated with a higher all-cause mortality and CVD mortality in patients with RA⁷⁶. Notably, this inverse association between BMI and mortality disappears after adjustment for co-morbidities and RA severity⁷⁷. Therefore, the obesity paradox of RA could relate to residual confounding and reverse causality whereby active inflammatory disease leads to unintentional weight loss⁷⁵. This hypothesis is supported by the finding that weight loss, rather than current BMI, is a strong

predictor of mortality in RA, with a fall in BMI of $\geq 1\text{kg/m}^2$ associated with almost twice the risk of death⁷⁸.

Although BMI is often used to define obesity, this index cannot provide any detail on body composition. Consideration of body composition might be important as individuals with an apparently 'normal' BMI ($< 25\text{ kg/m}^2$) can have different proportions of fat and lean mass, which might have cardiovascular effects. For example, women with RA have a lower lean mass but also an increased body fat mass compared with women without RA (termed at its extreme as 'sarcopenic obesity'), which is most apparent in women with a BMI in the normal range. Although data suggest a similar trend in men with RA, including greater odds of sarcopenia, high body fat, and a sarcopenic obesity phenotype compared with men without RA, this trend was not statistically significant or as pronounced as in women. This sex difference might relate to a higher prevalence of key predictors of sarcopenia (such as joint deformity and physical inactivity) in women than in men, as well as the possible influence of hormonal factors; however, the difference might also relate to the low statistical power of the findings⁷⁹.

Knowledge of the distribution of body fat might also be useful as an increased amount of ectopic adipose tissue is associated with a higher risk of CVD and metabolic diseases (in particular, type 2 diabetes)⁸⁰, and some evidence suggest that men with RA have a higher visceral adipose tissue area than men without RA, despite having a similar waist circumference and BMI⁸¹. Further research is needed to assess the true clinical implications of an altered body composition in RA. Notably, in clinical practice, BMI measurements dominate and few, if any, doctors regularly measure body composition of patients, probably because BMI is often considered together with other clinical information to help place the results into context. Furthermore, compared with weight measurements, measurements of body composition are less accurate and precise meaning that changes are harder to assess.

Psoriatic arthritis

Obesity is more prevalent in patients with PsA than in the general population⁸², which might contribute to an increased CVD risk in these patients. Obesity is strongly associated with an increased probability of developing PsA⁸³. For example, in a study of the UK general population, individuals with psoriasis and a BMI $\geq 35\text{kg/m}^2$ had a 48% higher risk of developing

PsA than individuals with psoriasis and a BMI $<25\text{kg/m}^2$, after adjustment for conventional risk factors⁸⁴. In a secondary analysis of all individuals, regardless of psoriasis status, having a BMI $\geq 35\text{kg/m}^2$ almost doubled the chance of an individual having PsA compared with individuals with a BMI $<25\text{kg/m}^2$. The associations between BMI and PsA are even more pronounced in other studies, including a reported 6-fold higher risk of developing PsA for women with a BMI $>35\text{kg/m}^2$ ⁸⁵.

Obesity seems to have a greater association with late-onset PsA or psoriasis and in individuals who are HLA-B27 haplotype negative⁸⁶. Notably, psoriasis has two peaks of onset: type I psoriasis (onset <40 years old) and type II psoriasis (onset >40 years old)^{87,88}. Comparing the pathogenesis of both subtypes, type I psoriasis seems to have a stronger genetic and autoimmune component (similar to type I diabetes mellitus), whereas type II psoriasis seems to have a stronger involvement of obesity (similar to type 2 diabetes mellitus⁸⁹). Additional studies are needed to examine these associations further.

Such associations do not prove causality and whether BMI is causally linked to PsA or psoriasis development cannot be ascertained from observational data alone. In 2019, researchers used genotyping (as a proxy for BMI measurements) of samples from the UK Biobank or HUNT study and a mendelian randomization approach to test for such a causal relationship. The data suggested that a higher BMI increased the risk of psoriasis (OR= 1.09 per 1 kg/m^2), with little evidence for causality in the opposite direction⁴. This directional association is supported by findings of improved disease activity in patients who had lost weight through dietary interventions^{5,6}. Indeed, a $\geq 5\%$ loss in body weight in patients starting treatments with TNF inhibitors, irrespective of the type of dietary intervention, predicted an achievement of minimal disease activity (MDA)⁵. In another study, the introduction of a very low energy diet (VLED; 640kcal/day) for 12-16 weeks in 41 patients with PsA and a BMI $\geq 33\text{ kg/m}^2$, which led to a median weight loss of 18.7 kg (18.6% of initial weight), resulted in 54% of the patients achieving MDA⁶. Interestingly, gastric bypass surgery is associated with a lower incidence of PsA (adjusted HR 0.29 (95% CI, 0.12-0.71)⁹⁰. Further prospective trials are needed to fully assess the effect of weight loss interventions on PsA outcomes.

Type 2 diabetes

The association between type 2 diabetes mellitus and CVD is well established. Type 2 diabetes mellitus is associated with an almost 200% higher risk of peripheral arterial disease, a 72% higher risk of ischaemic stroke and a 54% higher risk of non-fatal myocardial infarction than the general population⁹¹. Emerging evidence suggests that the incidence and prevalence of type 2 diabetes mellitus is higher in individuals with psoriatic disease than in the general population⁹², which contributes to a metabolic phenotype and increased risk of CVD in these patients. By contrast, whether type 2 diabetes mellitus is more common in RA is less clear.

Rheumatoid arthritis

The data on RA and type 2 diabetes mellitus are conflicting. In one report, the incidence of diabetes was higher in a cohort of 48,718 individuals with RA (incidence rate (IR) 8.6 per 1,000 person-years; 95% CI 8.5 – 8.7)) than in a cohort of 442,033 individuals without any known rheumatic disease (IR 5.8 per 1,000 person-years; 95% CI 5.8–5.8)), suggesting that individuals with RA have a ~50% higher risk of diabetes⁹³. However, the researchers of this study did not adjust for BMI. In a later study by Dubreuil et al.⁹², assessing the incidence of diabetes among individuals with PsA, psoriasis or RA, the risk of incident diabetes among the 11,158 individuals with RA was higher than in age-matched and sex-matched individuals without RA (unadjusted HR of 1.12; 95% CI 1.01–1.25); however, this increased risk was lost after adjusting for BMI, smoking and alcohol use (HR 0.94; 95% CI 0.84–1.06)⁹². Overall, as obesity is less common in patients with RA than in patients with PsA, links to metabolic dysfunction per se are less apparent.

Psoriatic arthritis

PsA is associated with higher incidence of type 2 diabetes. In the study by Dubreuil et al.⁹², the risk of new onset diabetes was 72% higher in the 4,196 individuals with PsA than in the age-matched and sex-matched individuals without psoriatic disease (HR 1.72; 95% CI 1.46–2.02)). Notably, adjustment for BMI, smoking, alcohol, baseline steroid use and co-morbidities attenuated this association (adjusted HR 1.33; 92% CI 1.09–1.61), highlighting the important contribution of obesity and lifestyle factors to diabetes risk in patients with PsA. A higher disease activity is also associated with a higher risk of developing diabetes in patients with PsA⁹⁴. Such work suggests PsA is a risk factor for Type 2 diabetes.

Similar to in the general population, several traditional risk factors including hypertension, dyslipidemia, and obesity are associated with an increased risk of type 2 diabetes in patients with PsA; interestingly, in one study, a later age of onset of psoriasis (>40 years) was more strongly linked to diabetes than a younger age of disease onset, implying the existence of potentially different disease phenotypes and supporting the argument that screening for diabetes is more informative in those individuals who develop psoriasis later in life⁹⁵.

Data from mouse models of psoriasis-like skin disease suggest a pathophysiological link between dysglycaemia and psoriatic disease. For example, in two such mouse models, inhibition of glucose uptake in keratinocytes through genetic or chemical inhibition of the GLUT1 transporter reduced skin inflammation and epidermal hyperproliferation⁹⁶, highlighting a potential future treatment strategy for psoriasis⁹⁶.

Non-alcoholic fatty liver disease

NAFLD includes a spectrum of liver diseases from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), and can include complications such as hepatic steatosis (accumulation of fat in the liver) and fibrosis (scarring of the liver) that eventually leads to cirrhosis and potentially carcinoma in a small number of individuals. NAFLD affects >20% of the general population and is associated with obesity and the development of type 2 diabetes mellitus⁹⁷.

Psoriatic disease is associated with an increased prevalence of NAFLD⁹⁸. In a cohort of 142 patients with psoriasis attending a health-care centre in Italy, 84 (59%) had evidence of NAFLD⁹⁹. NAFLD in these patients correlated with metabolic syndrome, obesity, hypertriglyceridemia, hypercholesterolaemia and PsA, providing further support for a strong metabolic phenotype in PsA. An increased risk of NAFLD in individuals with psoriasis was also reported in a meta-analysis of 7 case-control studies (OR: 2.15 95% CI: 1.57–2.94), even when only the high quality studies were analysed⁹⁸. The risk of NAFLD was higher in individuals with PsA than in individuals with psoriasis (OR: 2.25, 95% CI: 1.37–3.71), and was also higher in individuals with moderate to severe psoriasis than in individuals with mild psoriasis (OR: 2.07, 95% CI: 1.59–2.71).

Whether the occurrence of NAFLD in some individuals with PsA or RA is treatment-related or influenced by the severity of disease itself is unclear. In a comprehensive analysis of UK primary-care data analysing the risk of liver disease in patients prescribed or not prescribed a systemic therapy, compared with the general population, the risk of NAFLD was higher in patients with psoriasis, regardless of whether they were being treated with a systemic therapy (HR 1.18 and 2.23 for untreated and treated patients, respectively). NAFLD risk was also higher for treated patients with PsA (HR 2.11), with a trend towards greater risk in untreated patients with RA (HR 1.20)¹⁰⁰. Moreover, risks of cirrhosis were highest in treated patients with psoriasis and in untreated patients with PsA. These findings concur with a higher average BMI and a more pronounced metabolic perturbations (for example, excess liver fat) in patients with psoriasis or PsA than in patients with RA or the general population and also suggest such patients should be warned of their increased risk of liver disease and to keep alcohol intake to a minimum. The data should also help doctors encourage their patients to consider making even small but sustainable lifestyle changes to improve weight trajectories.

Blood pressure

Increased blood pressure is a causal risk factor of CVD, with a 10 mmHg reduction in systolic blood pressure associated with a 20% reduction in CVD events, a 17% reduction in CHD, a 27% reduction in stroke and a 28% reduction in heart failure risk¹⁰¹. Hence hypertension, defined as a blood pressure >140/90mmHg, potentially contributes to the risk of CVD in patients with RA or PsA.

Rheumatoid arthritis

Hypertension is a well-known cardiovascular risk factor in RA. In a large international cross-sectional study (the comorbidities in rheumatoid arthritis (COMORA) study) that included 4,586 patients with RA in 17 countries, the prevalence of hypertension in RA was estimated at 40.4%¹⁰². Data from UK Biobank suggested that individuals with self-reported RA have a 41% higher risk of hypertension compared with individuals without RA¹⁰³, which was attenuated to 19% after adjustment for conventional risk factors.

Overall, such evidence suggests that patients with RA have higher blood pressures than the general population, which could be because of the chronic effects of excess systemic cytokines on the structure of blood vessels and/or the effects of some therapies used to treat

RA. For example, an observational study of over 21,000 patients with RA reported that, compared with commencing methotrexate, commencing leflunomide was more strongly associated with a notable increase in blood pressure (SBP >20mmHg or DBP >10 mm Hg) (OR 1.37; 95% CI, 1.24–1.451), and an increased risk of developing hypertension (HR 1.52 (95% CI; 1.21–1.91))¹⁰⁴. By contrast, those patients starting methotrexate were 9% more likely to achieve an optimal blood pressure (<130/90 mmHg) after 6 months of treatment.

Psoriatic arthritis

Similar to RA, hypertension is more prevalent in patients with PsA than in the general population. In a prospective study of 648 patients with PsA (using data from the Canadian Community Health Survey), the prevalence of hypertension was higher than in the general population (standardised prevalence ratio 1.90; 95% CI 1.59-2.27)²³. In a separate meta-analysis, individuals with PsA were more than twice as likely to have hypertension than individuals without PsA (OR 2.07 (1.41-3.04))¹⁰⁵. However, interpretation of these findings is limited because of the substantial heterogeneity in the studies included in the analysis, including differences in study populations, outcome assessments and varying use of adjustments for confounders.

The exact mechanisms linking psoriatic disease and hypertension are unknown. Both conditions share several risk factors, including high BMI and smoking, but the association seems to remain even after adjustment for these factors. Higher quality studies, including the longitudinal measurement of blood pressure in patients with psoriasis of PsA, are needed to further investigate this relationship.

The effects of anti-rheumatic therapies

Systemic inflammation is central to RA, PsA and atherosclerosis pathogenesis. Therefore, minimising disease activity with effective anti-rheumatic therapies, which is recommended by current EULAR guidelines¹⁶, should lower the risk of cardiometabolic comorbidities (Box 1). The following section outlines the effect of current anti-rheumatic therapies on cardiometabolic outcomes (Box 2). Most evidence comes from observational pharmaco-epidemiology studies, principally of patients with RA as evidence for patients with PsA is more limited. Caution should always be applied when interpreting pharmaco-epidemiology studies

because of the potential for residual confounding and allocation bias, which is impossible to fully adjust for.

NSAIDs

Non-selective NSAIDs inhibit two recognised forms of cyclooxygenases (COX, also known as prostaglandin G/H synthase), COX1 and COX2, and include ibuprofen, naproxen, and diclofenac. These non-selective NSAIDs have anti-inflammatory effects, probably mediated by inhibition of COX2, and gastrointestinal adverse effects, mediated by inhibition of COX1. To avoid these adverse effects, selective COX2 inhibitors have also been developed, including etoricoxib and celecoxib¹⁰⁶.

NSAID therapy is associated with increased blood pressure, although this association might be specific to individual NSAIDs. For example, in one trial of patients with arthritis, treatment with ibuprofen increased the mean 24-hour systolic blood pressure (SBP) of the patients by 3.7mmHg, whereas celecoxib and naproxen had no effect¹⁰⁷.

NSAIDs, notably diclofenac (a non-selective COX inhibitor) and the selective COX-2 inhibitors rofecoxib and celecoxib, are associated with increased cardiovascular risk (such as myocardial infarction and CHD death), particularly at higher doses^{108,109}. Rofecoxib was withdrawn in 2004 because of safety concerns; in one randomised trial, treatment with this COX2 inhibitor was associated with almost twice the risk of cardiovascular thrombotic events compared with placebo treatment¹¹⁰. This increased risk could be caused by several effects mediated by COX2 inhibition including a reduction in prostacyclin concentrations, an increase in blood pressure, a decrease in angiogenesis and atherosclerotic plaque destabilization¹¹⁰. By contrast, a large well-conducted meta-analysis of trial data found that treatment with high-dose naproxen resulted in no excess risk of major cardiovascular events (relative risk 0.93; 95% CI 0.69–1.27)¹⁰⁹.

In a separate meta-analysis that included observational data, NSAID use was associated with an 18% higher risk of all cardiovascular events (CVEs) in patients with RA. The investigators concluded that COX2 inhibitors probably drove this effect, as the risk of CVE was not increased in a subgroup analysis of non-selective NSAIDs alone. In line with this supposition, in a study of over 17,000 patients with RA, treatment with rofecoxib or diclofenac was associated with

a notable increase in risk of CVD (HR 1.57 (95% CI 1.16-2.12) and HR 1.35 (95% CI 1.11-1.64), respectively), whereas other NSAIDs, including naproxen, ketoprofen and nabumetone, were not¹¹¹. Compared with studies in patients with RA, less is known about the effects of NSAIDs on CVD risk in patients with PsA.

Corticosteroids

Although corticosteroids are very effective at treating inflammation in patients with RA, these drugs have notable long-term effects on morbidity and mortality. Notably, long term use of oral steroids for any individual (whether or not they have RA) was associated with an 82% and 58% higher cardiovascular risk in women and men, respectively²⁰, which was likely in part related to the detrimental effects of these drugs on cardiometabolic factors. For example, corticosteroid use increases the risk of type 2 diabetes, hypertension, thrombotic stroke or myocardial infarction and death in patients with RA^{112,113}.

Some of the reported effects of steroid use on cardiovascular outcomes, however, could potentially be caused by confounding by indication and hence might disappear after correcting for disease activity¹¹⁴. Furthermore, in patients with active disease, some of these effects might be counteracted by the anti-inflammatory benefits of these drugs, such as a treatment-mediated reduction in underlying inflammation and improvement of mobility. To help address this question, a trial is underway (the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis Study (GLORIA) trial) to assess the safety profile of low doses of the corticosteroid prednisolone in patients with RA¹¹⁵. Notably though, in a previous study, high doses of prednisolone (≥ 8 mg daily) increased the cardiovascular mortality of patients with RA (HR 2.27 (95% CI 1.36–3.79), even after adjusting for propensity to receive glucocorticoids¹¹⁶.

Conventional synthetic DMARDs

Methotrexate use is associated with a 60% reduction in risk of all-cause mortality in patients with RA, including a notable reduction in risk of CVD mortality¹¹⁷. In one meta-analysis of observational studies of patients with RA, psoriasis or polyarthritis, methotrexate use was associated with a 21% lower risk of total CVD and a 18% lower risk of myocardial infarction¹¹⁸. This potential impact of methotrexate use was apparently greater after adjustment for disease severity (relative risk 0.64; 95% CI 0.43-0.96) and other concomitant medications

(relative risk 0.73; 95% CI 0.63-0.84). Similarly, in a systematic review, methotrexate use was associated with a 28% lower risk of all CVEs and a 19% lower risk of myocardial infarction in patients with RA¹¹⁹.

Taken at face value, these observational findings suggest that methotrexate use might reduce cardiovascular risk through dampening inflammation. However, in the CIRT trial, treatment with low-dose methotrexate did not reduce the rate of cardiovascular events in patients with established CVD, leading some to question whether methotrexate is cardioprotective. It should be noted though that the serum concentrations of CRP were substantially lower in the participants of CIRT than that reported for patients with RA or PsA³⁴.

Conventional synthetic DMARDs (csDMARDs) might also have metabolic effects, including altering body weight and risk of diabetes. For example, treatment with either methotrexate, prednisone or a TNF inhibitor is associated with weight gain, whereas leflunomide treatment is associated with modest weight loss in RA¹²⁰. In observation studies of patients with RA, those patients taking hydroxychloroquine or abatacept were less likely to develop diabetes, and those patients taking glucocorticoids were more likely to develop diabetes, than patients taking methotrexate monotherapy^{121,122}.

Small-molecule and biologic therapies

Anti-TNF therapy is effective at lowering inflammation and improving disease activity in patients with RA or PsA^{123,124}. As systemic inflammation drives cardiovascular risk in both conditions, TNF inhibition should also lower this risk.

In one observational study of patients with RA, the rate of myocardial infarction was similar in patients taking a TNF inhibitor to patients taking csDMARDs (after adjustment for baseline risk factors)¹²⁵. However, the rate of myocardial infarction was 64% lower in the patients who clinically responded to anti-TNF therapy within 6 months than the anti-TNF non-responders, consistent with the notion that suppressing inflammation might lower cardiovascular risk. Unfortunately, the investigators did not assess DAS28 scores at 6 months in the patients undergoing csDMARD therapy, preventing the assessment of whether lowering RA disease

activity per se was associated with a decreased incidence of myocardial infarction, or whether this effect was specific to anti-TNF therapy.

In a meta-analysis, anti-TNF therapy was associated with a 54% lower risk of all CVEs, a 19% lower risk of myocardial infarction and a 31% lower risk of stroke compared with csDMARD therapy in patients with RA¹²⁶. This meta-analysis had a few limitations (including analysis of a small number of studies, many of which were observational in design, and a high clinical and methodological heterogeneity); however, similar findings were reported in a larger meta-analysis, with anti-TNF inhibitor use being associated with a lower risk of all CVEs, myocardial infarction, strokes and major adverse cardiac events in patients with RA¹¹⁹.

In addition to TNF inhibitors, other biologic drugs are also effective at targeting inflammation in RA, including abatacept (a co-stimulation inhibitor) and tocilizumab (an IL-6 receptor blocker). In one comparison of the cardiovascular effects of various biologic drugs in older patients with RA (mean age 64 years), the risk of acute myocardial infarction was higher among patients initiating treatment with an anti-TNF inhibitor, in particular etanercept or infliximab, compared with patients initiating treatment with abatacept¹²⁷. By contrast, the risk of CHD was similar for patients being treated with tocilizumab compared with patients being treated with abatacept. However, these findings should be interpreted with caution owing to the retrospective design of the study, the small event numbers in some of the groups and the lack of RA disease severity markers. Such limitations might have confounded the results for certain biologics; for example, a preferential use of anti-TNF therapy for patients with severe disease might have resulted in an overall higher disease activity in this group than in the other groups. The lipid profiles of the patients were also not reported in the study, which is important as a risk-associated lipid profile might have influenced the decision to prescribe tocilizumab and potentially caused selection bias (that is, clinicians might have been less likely to prescribe this therapy in patients with existing hyperlipidaemia and/or increased CVD risk).

Some therapies for RA can also have metabolic effects. For example, treatment with tocilizumab or tofacitinib in patients with RA is associated with an increase in total cholesterol and LDL-C concentrations towards that of individuals without RA, probably owing to IL-6

inhibition^{60,64}. Whether this effect is part of a compensatory response to dampened inflammation or has long-term cardiovascular sequelae remains to be fully determined. However, in a short observational study (mean follow up <1year), the cardiovascular risk of patients undergoing treatment with a TNF inhibitor was similar to patients who had switched to tocilizumab¹²⁸. Furthermore, in a prospective phase IV cardiovascular outcome trial (ENTRACTE), the risk of incident MACE was the same for patients undergoing tocilizumab treatment and for those undergoing etanercept treatment (HR 1.05, CI 0.77 to 1.43)¹²⁹. TNF inhibition is also potentially associated with a lower risk of new onset diabetes mellitus than csDMARD therapy in patients with RA or psoriasis¹³⁰. For patients with RA or ankylosing spondylitis, some evidence suggest that TNF-inhibition might result in a gain in weight, with a shift to the visceral region¹³¹. However, this study included only 20 patients with no control group. Hence, further studies in this area, including the potential CVD consequences of TNF inhibition, are needed.

Unlike therapies for RA, evidence of the effect of novel therapies for PsA on cardiometabolic outcomes are limited. Treatment with apremilast (an oral phosphodiesterase-4 (PDE-4) inhibitor) is associated with modest weight loss^{132,133}. A clinical trial (The Immune Metabolic Associations in Psoriatic Arthritis (IMAPA) study) is currently underway to investigate the cardiometabolic and immune effects of apremilast in patients with PsA¹³⁴. In terms of IL-17 inhibition, 52 weeks of secukinumab treatment improved flow-mediated dilation (FMD) in patients with psoriasis¹³⁵. However, FMD is only a weak surrogate marker of future risk of CVD, and is not accepted as such by licensing authorities; formal trials of cardiovascular outcome with these newer agents are currently lacking.

Conclusions

The notion that patients with RA have an excess risk of CVD, even after accounting for traditional risk factors, is now well-established. Overwhelming evidence support the idea that systemic inflammation drives this excess risk both directly and by affecting several other risk factors. With the decline of steroid use and emergence of better treatment options in RA, CVD risk should fall over time. However, the relevance of the rise in LDL-C concentration following treatment with some anti-rheumatic drugs remains uncertain. Clinically, CVD risk

scoring should now be a regular part of RA management, taking advantage of the RA multiplier in risk scores. Modifiable CVD risk factors, including dyslipidaemia and blood pressure, should be managed as aggressively in patients with RA as in the general population. Notably blood pressure targets in individuals with an increased cardiovascular risk are now even lower than before¹³⁶.

In PsA, evidence supporting excess cardiovascular risk in patients is limited; although, some evidence suggest that for patients with severe disease, CVD risk might reach the same extent as in RA. Clinical judgement is needed for deciding when to use a CVD risk multiplier. Obesity and associated metabolic outcomes (such as diabetes and NAFLD) are more common in patients with PsA than in the general population. Multiple strands of evidence also support the contribution of obesity to the pathophysiological process in some patients with PsA, particularly in late-onset disease, with weight loss being associated with a lower disease activity. Accordingly, more work is needed to investigate the clinical benefits of different weight loss strategies in this condition.

In terms of the effect of anti-rheumatic therapies, the majority of evidence, albeit predominantly observational in nature, suggests that treatment with a TNF inhibitor or methotrexate lowers the risk of CVD, whereas treatment with corticosteroids or some NSAIDs increases the risk of CVD in patients with RA. Some evidence suggests that CVD risk varies depending on the biologic used, but this notion requires further study. Targeting inflammation with biologics or methotrexate might therefore have positive cardiovascular effects in RA, supporting the idea that the systemic inflammatory response might be causally linked to CVD. However, the effect of targeting inflammation in PsA on cardiometabolic outcomes requires further study.

Overall, these findings highlight the importance of a holistic, multisystem approach to the management of RA and PsA, not only to lessen clinically evident joint and/or skin-associated disease but also to improve life expectancy and quality of life.

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Review Criteria

A search for studies published up to January 2019 and focusing on cardiometabolic comorbidities in rheumatoid and psoriatic arthritis was performed in PubMed. The search terms used were “rheumatoid arthritis” or “psoriatic arthritis” with either “cardiometabolic”, “cardiovascular”, “dyslipidaemia”, “adiposity”, “diabetes”, “NAFLD”, “blood pressure”, “hypertension”, “DMARDs”, “TNF-inhibitors”, “corticosteroids”, or “NSAIDs”. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

Key points

- Cardio-metabolic comorbidities represent a notable morbidity and mortality burden in patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA)
- Patients with RA have a higher risk of cardiovascular disease (CVD) than individuals of the general population; however, some of this increased risk might be driven by steroid use.
- PsA is more strongly linked to metabolic co-morbidities, including obesity, NAFLD and type 2 diabetes mellitus.
- Dampening inflammation with methotrexate or TNF-inhibitors might lower the cardiovascular risk of patients with RA, but formal randomised controlled trials are currently sparse.
- In PsA, weight loss might reduce disease severity and/or risk of PsA development, but future prospective studies are needed to assess the effects of lifestyle interventions and/or pharmacologically-induced weight loss.
- Clinical trials assessing the long-term effects of new drugs for treatment of RA or PsA on cardiovascular outcomes are warranted, including the safety and benefits of these treatments.

Box 1: Treatment strategies for cardiometabolic comorbidities in RA and PsA

Rheumatoid arthritis

- Treat systemic inflammation with conventional synthetic DMARDs and biologic drugs
- Assess cardiovascular risk factors, including non-fasting lipids levels and blood pressure, and manage modifiable risk factors when absolute CVD risk, as assessed by an appropriate risk prediction algorithm, is above target thresholds, or single risk factors are sufficiently high to merit treatment.

Psoriatic arthritis

- Treat underlying systemic inflammation with conventional synthetic DMARDs and biologic drugs
- Consider the use of weight loss interventions, particularly in those overweight or obese

- Consider to screen for diabetes if the patient is not known to have diabetes and has not been recently tested.
- Continue to address traditional CVD risk factors and treat when the absolute CVD risk is above target threshold

Box 2. Effect of anti-rheumatic therapies on cardiometabolic outcomes

NSAIDs

- NSAID use can increase systolic blood pressure (SBP) and overall cardiovascular risk; however, this effect might depend on the NSAID used¹⁰⁷.
- Ibuprofen use is associated with increased SBP in patients with rheumatoid arthritis (RA) or osteoarthritis¹⁰⁷.
- Treatment with diclofenac or rofecoxib (now withdrawn) is associated with an increased risk of cardiovascular disease (CVD) in patients with RA¹⁰⁹.
- Treatment with naproxen was not associated with an increased risk of CVD in RA or the general population¹¹¹.

Corticosteroids

- In the general population, corticosteroid use is associated with increased SBP, weight, insulin resistance, cardiovascular risk and all-cause mortality^{112,113}.

Conventional synthetic DMARDs (csDMARDs)

- Methotrexate use has been associated with a lower cardiovascular risk and a lower all-cause mortality in observational studies of patients with RA¹¹⁷.
- Treatment with leflunomide or apremilast is associated with modest weight loss in individuals with RA or PsA, respectively, compared with treatment with other csDMARDs^{120,132,133}.
- The risk of developing diabetes seems lower with hydroxychloroquine use than with methotrexate use in patients with RA^{121,122}. Ongoing trials are testing the effects of hydroxychloroquine on cardiovascular outcomes¹³⁷

Biologic drugs and small molecule inhibitors

- The risk of CVD in patients with RA seems to be lower for patients undergoing TNF-inhibitor therapy than for patients undergoing csDMARD therapy¹²⁶.
- Treatment with either tocilizumab or tofacitinib is associated with increased concentrations of LDL-cholesterol^{60,64}; larger clinical trials are needed to determine the long-term cardiovascular effects of such lipid changes.

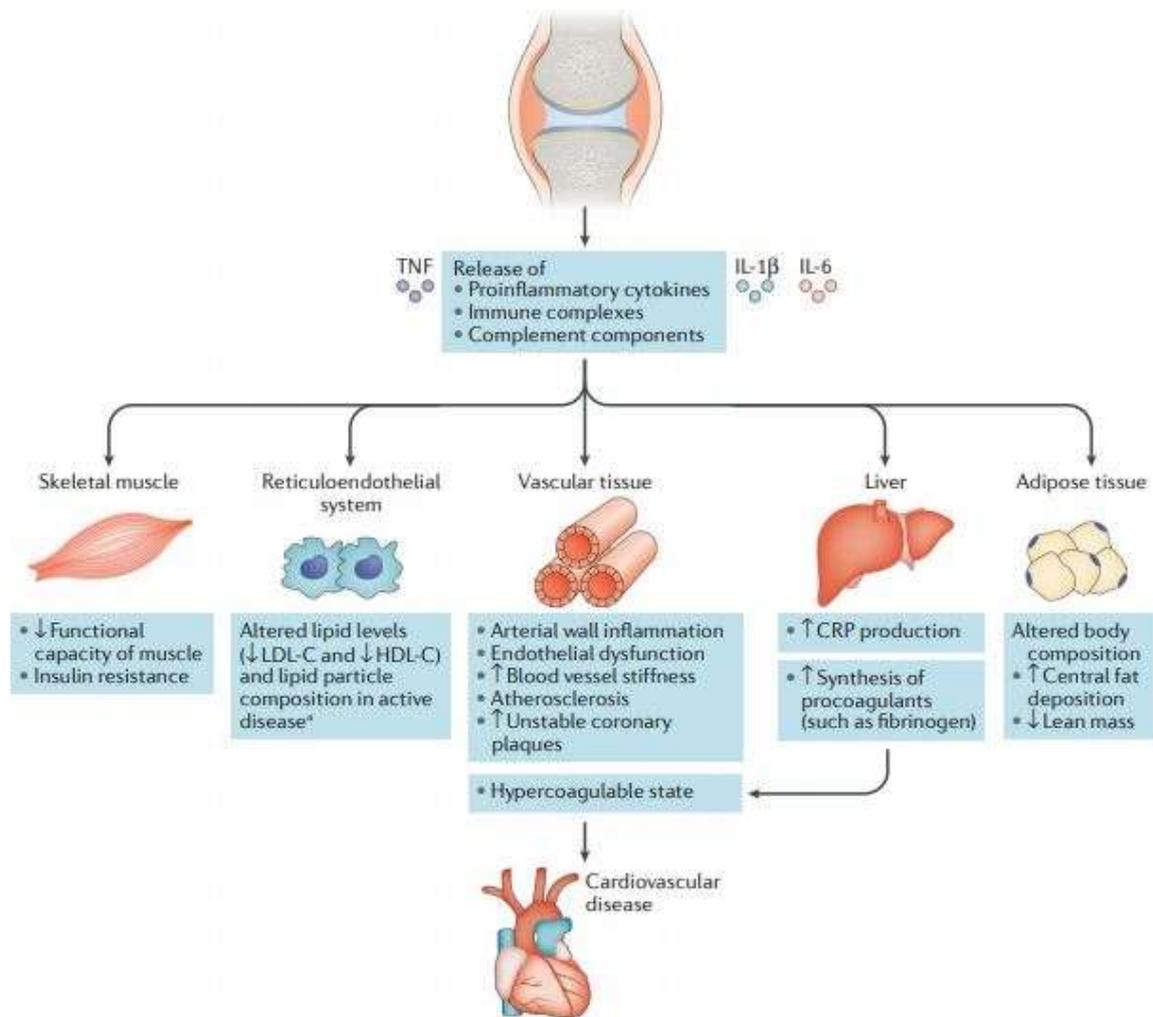


Figure 1. Potential relationship between systemic inflammation in RA and PsA and cardiovascular risk

Several pro-inflammatory cytokines, including TNF, IL-1 β and IL-6, chemokines and immune complexes are released into the circulation from the synovial tissue, bone marrow of inflamed joints or associated lymph nodes. These molecules affect a number of distant tissues. Damage to the vascular tissue can result in arterial wall inflammation, endothelial dysfunction and arterial stiffness, which are, collectively, markers of subclinical damage and precursors to atherosclerosis and, ultimately, coronary heart disease. Increased systemic cytokines can directly impede insulin-mediated glucose uptake in skeletal muscle and cause skeletal muscle atrophy, impairing the functional capacity of the muscles and potentially leading to insulin resistance. Systemic inflammation might contribute to altered body composition, including increased central fat deposition and reduced lean mass. IL-6 production in rheumatoid arthritis (RA) can increase the synthesis of fibrinogen and other procoagulants in the liver,

contributing to a hypercoagulable state. Finally, although high-grade systemic inflammation results in a meaningful decline in circulating LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) concentrations, some evidence suggests that these changes are caused by increased peripheral catabolism of lipids, presumably by cells of the activated reticuloendothelial system. There are also multiple qualitative changes in lipids. The relevance of such inflammation-associated lipid changes to cardiovascular risk in these conditions is not well established. ^aSome drugs influence lipid levels, but the impact this influence has on cardiovascular disease risk is uncertain. CRP, C-reactive protein; PsA, psoriatic arthritis.

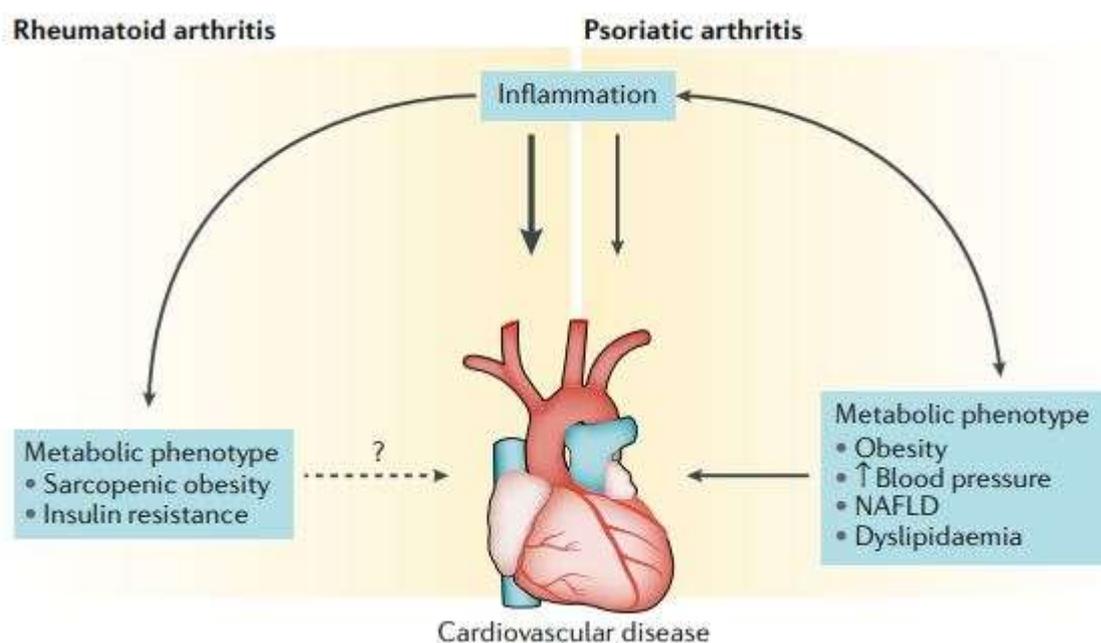


Figure 2. Potential relationship between cardiovascular and metabolic comorbidities in RA and PsA

Both rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are characterized by systemic inflammation, which can contribute to an increased risk of cardiovascular disease (CVD) and metabolic disturbances. RA is associated with a high risk of CVD, probably owing more to chronic systemic inflammation than metabolic disturbances per se, but the impact of changes in body composition or insulin resistance on CVD risk is uncertain. By contrast, PsA is strongly associated with a dysfunctional metabolic profile (such as obesity and increased risk of type 2 diabetes mellitus), particularly in patients who develop the disease in later life, which might indirectly increase the risk of CVD in these patients. However, individuals who develop PsA at

a younger age might have a larger inflammatory drive and a less obvious metabolic phenotype than patients with an older age of disease onset, and so inflammation might be relatively more important to CVD risk in these patients. NAFLD, non-alcoholic fatty liver disease.

Table 1. Cardio-metabolic comorbidities in rheumatoid arthritis and psoriatic arthritis

| Cardio-metabolic comorbidities | Rheumatoid arthritis | Psoriatic arthritis | References |
|---|-----------------------------|----------------------------|-------------------|
| Cardio-metabolic outcomes^a | | | |
| Risk of CVD | ++ | + | 1,10,11,21 |
| Obesity | +/- | ++ | 4,73,74,79,84 |
| Type 2 diabetes | +/- | ++ | 92–95 |
| Hypertension | + | + | 23,102,103,105 |
| NAFLD | +/- | ++ | 98–100 |
| Lipid profiles in patients with active disease^b | | | |
| Total cholesterol | ↓ | ↓ | 57,58 |
| LDL-C | ↓ | ↓ | 57,61 |

| | | | |
|--------------|---|---|-------|
| HDL-C | ↓ | ↓ | 58,66 |
|--------------|---|---|-------|

^aCompared with individuals of the general population

^bCompared with individuals in remission or without disease

++ markedly increased; + increased; +/- mixed evidence.

↑ increased; ↓ decreased.

Rheumatoid arthritis (RA); Psoriatic arthritis (PsA); Cardiovascular disease (CVD); Body Mass Index (BMI); Non Alcoholic Fatty Liver Disease (NAFLD); low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C).