International Journal of Cardiology 178 (2015) 191–199

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Ischemic cardiovascular involvement in psoriasis: A systematic review

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ARTICLE INFO

Article history:
Received 27 August 2014
Accepted 21 October 2014
Available online 23 October 2014

Keywords:
Psoriasis
Cardiovascular risk
Atherosclerosis
Coronary artery disease
Inflammation

ABSTRACT

Epidemiologic studies demonstrate that psoriasis is associated with shorter life expectancy, most frequently attributable to cardiovascular (CV) events. Although increased prevalence and incidence of CV risk factors for atherosclerosis have been reported in psoriatic patients, psoriasis likely plays an independent role in the increased cardiovascular risk, presumably linked to the chronic systemic inflammatory state. Consistently, preliminary investigations suggest that anti-inflammatory therapies may improve early subclinical vascular alterations and reduce cardiovascular morbidity and mortality.

This review will focus on ischemic CV involvement in psoriatic patients, summarizing the prevalence and incidence of CV risk factors and CV events, as well as evidence on mechanisms of premature atherosclerosis and on effects of systemic anti-inflammatory therapies on CV risk profile.

We performed a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and evaluated the quality of studies comparing drug treatments using Detsky score.

Our review documented that psoriatic patients are at increased CV risk, related to raised prevalence and incidence of CV risk factor and to inflammatory status. However, available literature lacks of studies that establish appropriate targets for CV risk factors and assess the clinical value of screening for subclinical organ damage and the impact of disease-modifying therapies on CV risk profile in psoriatic patients. Awareness of raised CV risk in psoriatic patients should foster further research aimed at elucidating these aspects.

1. Introduction

Psoriasis is a common and chronic inflammatory disorder of the skin characterized by hyperproliferative epidermis and cutaneous lymphocytic infiltrate that can **involve** also joints causing a form of arthritis, known as Psoriatic Arthritis (PsA). The etiology of psoriasis is still unknown, but evidence suggest that it is a complex disorder caused by the interaction among multiple genes, the immune system and environmental factors [1].

Epidemiologic studies demonstrated that morbidity and mortality in psoriatic patients are mainly due to cardiovascular (CV) diseases including myocardial infarction (MI), stroke and peripheral arterial disease [2–8]. Compared with unaffected individuals, higher prevalence and incidence of CV risk factors have been reported in psoriatic patients [9–13]. This observation, however, does not fully explain the increased CV risk. Similar to other inflammatory diseases [14,15], immune system activation, involving T helper (Th)-1, Th-17, regulatory T cells and inflammatory cytokines, plays a key role in all stages of the atherothrombotic process and might substantially contribute to CV risk in psoriasis [16].

This review will focus on ischemic CV involvement in psoriatic patients, summarizing the prevalence and incidence of CV risk factors and CV events, as well as evidence on mechanisms of premature atherosclerosis and on effects of systemic anti-inflammatory therapies on CV risk profile.

2. Methodology of research

2.1. Search strategy and study selection

We reviewed studies, identified by electronic database searches, combining MESH terms related to CV involvement in psoriasis. After application of filters, 53 articles were considered for the purpose of this systematic review, performed using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 guidelines [17]. The PRISMA flow-chart of studies included is displayed in Fig. 1. The evaluation of quality of studies comparing drug treatments was

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http://dx.doi.org/10.1016/j.ijcard.2014.10.092
0167-5273/

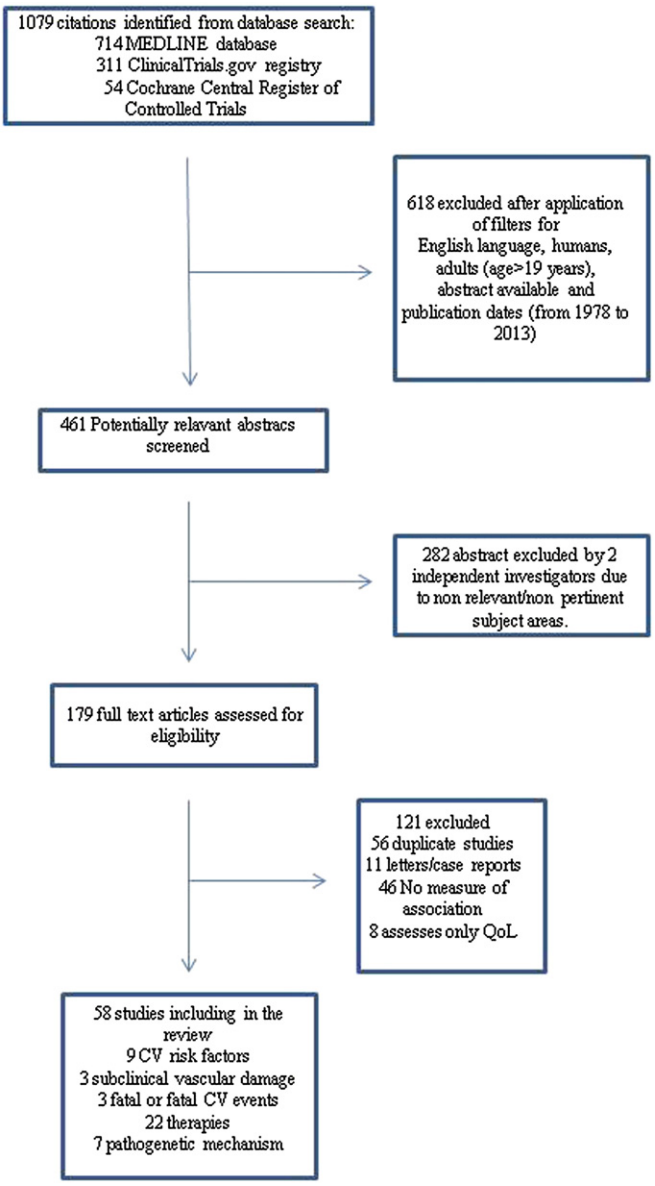

Fig. 1. The PRISMA flowchart of studies included in the systematic review.

performed using Detsky score [18] and the results are reported in Table 1. Complete search study, study selection and quality assessment are presented as supplemental material.

3. "Classical" CV risk factors in psoriatic patients

3.1. Dyslipidemia

Abnormalities of lipid metabolism have frequently been reported in psoriatic patients and likely contribute to the development of atherosclerosis [12]. A recent systematic review of 25 studies reported higher incidence of dyslipidemia compared to controls and an increased prevalence of lipid abnormalities, with odds ratio (OR) ranging from 1.04 to 5.55, depending on the severity of the disease. However, in most studies results were not controlled for concomitant drug use, reducing the association strength, whereas incidence of dyslipidemia was available in very few studies [19]. The inflammatory milieu characterizing psoriasis might mechanistically explain the increased prevalence of dyslipidemia in psoriatic patients, since cytokines commonly expressed in these patients have also been implicated in lipid abnormalities. In fact, TNF α, IL-1 and IL-6 have been shown to inhibit lipoprotein lipase activity, decreasing TG clearance [20] whereas other studies suggest that these cytokines may increase lipolysis and prompt hepatic de novo fatty acid synthesis, resulting in elevated lipid levels [21]. Yet, it is unknown whether treatment of lipid disorders in psoriatic patients reduces CV risk or affects the natural course of the disease.

3.2. Insulin resistance (IR) and diabetes mellitus (DM)

Impaired fasting glycemia, glucose intolerance and DM are frequently associated with psoriasis, in particular among patients with severe disease [9]. The meta-analysis of 27 studies by Armstrong et al. [9] reported increased DM prevalence in psoriatic patients with an overall OR of 1.59 (95% confidence interval (CI), 1.38–1.83), varying from 1.53 (1.16–2.04) for mild to 1.97 (1.48–2.62) for severe psoriasis. In 5 studies assessing incidence, psoriasis was associated with a relative risk (RR) of 1.27 (1.16–1.40) of developing DM. Notably, the increased incidence of DM in psoriasis holds after controlling for CV risk factors [11], although no adjustment could be made for further relevant potential confounders, including systemic adsorption of topical corticosteroids.

3.3. Arterial hypertension

A recent systematic review and meta-analysis of 24 studies reported that psoriasis is associated with increased prevalence of hypertension with an OR of 1.30 (1.15–1.47) among patients with mild and of 1.49 (95% CI, 1.20–1.86) among those with severe disease. Incidence of hypertension was also higher in psoriatic patients and correlated to the severity of disease (hazard ratio (HR) of 1.07 and 1.17 for mild and severe disease, respectively). Notably, in PsA patients OR was higher (2.07; 1.41–3.04) [10]. However, most studies in this meta-analysis did not fully adjust for smoking and obesity that are quite prevalent in psoriatic patients, limiting the observation strength.

3.4. Obesity

Recent systematic review and meta-analysis of 16 studies indicate that compared to controls the prevalence of obesity is increased in psoriatic patients with an OR of 1.66 (1.46–1.89), varying from 1.46 in patients with mild to 2.23 in those with severe disease [13]. Reducing weight in obese psoriatic patients may have beneficial effects on obesity-associated comorbidities and disease severity. In fact, a recent trial demonstrated that in obese psoriatic patients, an energy-restricted diet increasing n−3 and reducing n−6 polyunsaturated fatty acids, ameliorated metabolic profile and the response to immune-modulating therapy, improving the disease course [22].

Evidence from observational studies and meta-analyses indicate a substantial higher prevalence of DM, hypertension and obesity among psoriatic patients but obviously cannot elucidate the mechanistic links subtending this association. Although it is conceivable that chronic inflammatory activation may represent a common pathogenetic mechanism explaining the associations between psoriasis and DM and hypertension and obesity, additional studies are warranted to further investigate whether these associations are independent on the presence of confounders including smoking, physical inactivity and anti-psoriatic drugs use. In addition, only few studies reported the incidence of these co-morbidities in psoriatic patients.

4. Subclinical vascular damage: carotid intima-media thickness (IMT) and endothelial dysfunction (ED)

Several studies showed early vascular abnormalities in psoriasis, represented by impaired flow-mediated vasodilation (FMD) of brachial artery and increased IMT of common carotid artery. Balci et al. [23] compared subclinical atherosclerosis of the carotid and brachial arteries in 43 psoriatic patients without CV risk factors and 43 matched healthy controls. In psoriatic patients, mean IMT values of the right, left and