



Review

Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment

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Abstract: Psoriasis is a common and chronic inflammatory disease of the skin. It may impair the physical and psychosocial function of patients and lead to decreased quality of life. Traditionally, psoriasis has been regarded as a disease affecting only the skin and joints. More recently, studies have shown that psoriasis is a systemic inflammatory disorder which can be associated with various comorbidities. In particular, psoriasis is associated with an increased risk of developing severe vascular events such as myocardial infarction and stroke. In addition, the prevalence rates of cardiovascular risk factors are increased, including hypertension, diabetes mellitus, dyslipidemia, obesity, and metabolic syndrome. Consequently, mortality rates have been found to be increased and life expectancy decreased in patients with psoriasis, as compared to the general population. Various studies have also shown that systemic treatments for psoriasis, including methotrexate and tumor necrosis factor- α inhibitors, may significantly decrease cardiovascular risk. Mechanistically, the presence of common inflammatory pathways, secretion of adipokines, insulin resistance, angiogenesis, oxidative stress, microparticles, and hypercoagulability may explain the association between psoriasis and cardiometabolic disorders. In this article, we review the evidence regarding the association between psoriasis and cardiovascular comorbidities, focusing on severe vascular events, cardiovascular risk factors and implications for treatment.

Keywords: psoriasis; cardiovascular disease; cerebrovascular disease; atherosclerosis; hypertension; diabetes mellitus; obesity; dyslipidemia; metabolic syndrome; systemic inflammation

1. Introduction

Psoriasis is a common and chronic inflammatory disease, and may cause significant impairment to the patient's quality of life [1,2]. Traditionally, psoriasis has been regarded as a disease affecting only the skin and joints. In recent years, studies from different countries have shown that psoriasis is a systemic inflammatory disease, which is often associated with various comorbidities. In particular, there is a greater risk of developing severe vascular events such as cardiovascular and cerebrovascular diseases [3–7]. In addition, the prevalence rates of cardiovascular risk factors are increased in psoriasis patients, including hypertension, diabetes, obesity, dyslipidemia, subclinical atherosclerosis, and smoking [8–10]. It has been proposed that systemic inflammation may provide a mechanistic link between psoriasis and cardiometabolic disorders.

Some studies have also investigated the relationship between the severity of psoriasis and the risk of cardiovascular comorbidities. The definition of severe psoriasis varies in different studies. In some studies (particularly large-scale epidemiological studies), patients were classified as severe psoriasis if they required systemic therapy (including methotrexate, retinoid, cyclosporine, biological agents,

or phototherapy) [3,11,12]. In other studies, severe psoriasis was defined in terms of Psoriasis Area and Severity Index score (for example, PASI > 15) [13], or body surface area involvement (for example, BSA > 10%) [14,15].

Previous studies have shown that mortality rates are increased in psoriasis patients compared to healthy controls [16–18], and the life expectancy of patients with moderate to severe psoriasis is decreased by approximately 5 years, mainly due to cardiovascular comorbidities [19]. Furthermore, the presence of cardiovascular comorbidities in patients with psoriasis has been found to be associated with greatly increased economic and healthcare burden [20,21]. Therefore, physicians should be aware of the cardiovascular risk in patients with psoriasis, and administer appropriate treatments to prevent the future development of vascular events.

2. Psoriasis and Severe Vascular Events

A large number of epidemiological studies performed in various countries have demonstrated that psoriasis is associated with increased prevalence of cardiovascular diseases [22–24]. A large-scale population-based epidemiological study performed in the United Kingdom using the General Practice Research Database demonstrated that the risk of myocardial infarction is increased in patients with psoriasis [3]. Moreover, there was an association between the risk of myocardial infarction and psoriasis disease severity. The relative risk was greater in younger patients, but the risk was still significantly increased in elderly patients who were 60 years of age. Another population-based cohort study performed in the United Kingdom found increased risk of major adverse cardiovascular events (including myocardial infarction, stroke and cardiovascular mortality) in patients with psoriasis [25]. Epidemiological studies in the United States and Canada have also demonstrated that psoriasis patients have a higher risk of developing myocardial infarction [26–29]. Population-based studies performed in Denmark found that the risk of myocardial infarction is increased in patients with severe psoriasis but not mild psoriasis [12]. A population-based study in Taiwan found an increased risk of myocardial infarction in patients with psoriasis [30]. An epidemiological study in Japan also showed an association between psoriasis and coronary heart disease [31]. In addition, a cohort study from the United Kingdom revealed that the life expectancy of patients with severe psoriasis is reduced by about 6 years, mainly as a result of cardiovascular mortality [32]. On the other hand, a few studies in certain populations found no significant association between psoriasis and risk of cardiovascular disease [33–35].

Moreover, patients with psoriasis were shown to have an increased risk of developing cerebrovascular disease (stroke), which correlates with the severity of psoriasis disease [8,11,24,36–42]. On the other hand, some studies found no significant association between psoriasis and cerebrovascular disease [27,43–45]. These discrepancies in findings may be due to differences in the study population and the methodology used. A recent meta-analysis found that the risk of stroke (expressed in terms of the hazard ratio) was 1.10 and 1.38 for mild and severe psoriasis, respectively, and the risk of myocardial infarction (expressed in terms of the hazard ratio) was 1.20 and 1.70 for mild and severe psoriasis, respectively [46]. Another meta-analysis found that the risk ratios for stroke were 1.12 for mild psoriasis and 1.56 for severe psoriasis [24]. The findings from studies investigating the risk of severe vascular events (including myocardial infarction, cerebrovascular disease, and cardiovascular death) in patients with psoriasis are summarized in Table 1.

Table 1. Studies investigating the risk of severe vascular events (including myocardial infarction, cerebrovascular disease, and cardiovascular death) in patients with psoriasis.

Study	Cardiovascular Comorbidities	Number of Patients/Controls	Relative Risk	Population/Type of Study
Abuabara et al., 2010 [32]	Cardiovascular death	Severe psoriasis: 3603; Controls: 14,330	Hazard ratio: 1.57 (95% CI 1.26–1.96)	United Kingdom/Cohort study
Ahlehoff et al., 2011 [41]	Composite endpoint (myocardial infarction, stroke and cardiovascular death)	Mild psoriasis: 34,371; Severe psoriasis: 2621; Controls: 4,003,265	Rate ratio: Composite endpoint: Mild psoriasis: 1.20 (95% CI 1.14–1.25); Severe psoriasis: 1.58 (95% CI 1.36–1.82); Stroke: Mild psoriasis: 1.25 (95% CI 1.16–1.33); Severe psoriasis: 1.71 (95% CI 1.39–2.11); Myocardial infarction: Mild psoriasis: 1.22 (95% CI 1.12–1.33); Severe psoriasis: 1.45 (95% CI 1.10–1.90); Cardiovascular death: Mild psoriasis: 1.14 (95% CI 1.06–1.22); Severe psoriasis: 1.57 (95% CI 1.27–1.94)	Denmark/Cohort study
Ahlehoff et al., 2011 [47]	Composite cardiovascular endpoint (recurrent myocardial infarction, stroke and cardiovascular death) after first time myocardial infarction	Patients with first time myocardial infarction; Psoriasis: 462; Controls: 48,935	Hazard ratio: 1.26 (95% CI 1.06–1.54)	Denmark/Cohort study
Ahlehoff et al., 2012 [40]	Ischemic stroke	Mild psoriasis: 36,765; Severe psoriasis: 2793; Controls: 4,478,926	Rate ratio: Age < 50 years: Mild psoriasis: 1.97 (95% CI 1.66–2.34); Severe psoriasis: 2.80 (95% CI 1.81–4.34); Age ≥ 50 years: Mild psoriasis: 1.13 (95% CI 1.04–1.21); Severe psoriasis: 1.34 (95% CI 1.04–1.71)	Denmark/Cohort study

Table 1. Cont.

Study	Cardiovascular Comorbidities	Number of Patients/Controls	Relative Risk	Population/Type of Study
Brauchli et al., 2009 [44]	Myocardial infarction, stroke or transient ischemic attack	Psoriasis: 36,702; Controls: 36,702	<p>Odds ratio:</p> <p>Myocardial infarction: Overall: 1.14 (95% CI 0.93–1.41); Age < 60 years: 1.66 (95% CI 1.03–2.66); Age ≥ 60 years: 0.99 (95% CI 0.77–1.26);</p> <p>Stroke: Overall: 0.93 (95% CI 0.77–1.13); Age < 60 years: 0.52 (95% CI 0.29–0.93); Age ≥ 60 years: 0.99 (95% CI 0.80–1.22);</p> <p>Transient ischemic attack: Overall: 1.00 (95% CI 0.81–1.25); Age < 60 years: 1.28 (95% CI 0.61–2.68); Age ≥ 60 years: 1.02 (95% CI 0.80–1.29)</p>	United Kingdom/Inception cohort study with nested case-control analysis
Chiang et al., 2012 [39]	Ischemic stroke	Psoriasis: 2783; Controls: 13,910	Hazard ratio: 1.27 (95% CI 1.05–1.52)	Taiwan/Retrospective cohort study
Dowlathshahi et al., 2013 [35]	Cardiovascular disease (coronary heart disease, stroke, heart failure)	Psoriasis: 262; Controls: 8009	Hazard ratio: 0.73 (95% CI 0.50–1.06)	Netherlands/Prospective cohort study
Dregan et al., 2014 [45]	Coronary heart disease Stroke	Severe psoriasis: 5648; Mild psoriasis: 85,232; Controls: 373,851	<p>Hazard ratio:</p> <p>Mild psoriasis: Stroke: 1.08 (95% CI 0.98–1.18); Coronary heart disease: 1.03 (95% CI 0.97–1.11);</p> <p>Severe psoriasis: Stroke: 0.93 (95% CI 0.64–1.36); Coronary heart disease: 1.29 (95% CI 1.01–1.64)</p>	United Kingdom/Cohort study
Egeberg et al., 2017 [12]	Myocardial infarction	Mild psoriasis: 49,646; Severe psoriasis: 11,957; Controls: 4,300,085	<p>Hazard ratio:</p> <p>Mild psoriasis: 1.02 (95% CI 0.96–1.09); Severe psoriasis: 1.21 (95% CI 1.07–1.37)</p>	Denmark/Cohort study
Gelfand et al., 2006 [3]	Myocardial infarction	Mild psoriasis: 127,139; Severe psoriasis: 3837; Controls: 556,995	<p>Relative risk:</p> <p>30-year-old: Mild psoriasis: 1.29 (95% CI 1.14–1.46); Severe psoriasis: 3.10 (95% CI 1.98–4.86);</p> <p>60-year-old: Mild psoriasis: 1.08 (95% CI 1.03–1.13); Severe psoriasis: 1.36 (95% CI 1.13–1.64)</p>	United Kingdom/Prospective cohort study

Table 1. Cont.

Study	Cardiovascular Comorbidities	Number of Patients/Controls	Relative Risk	Population/Type of Study
Gelfand et al., 2009 [11]	Stroke	Mild psoriasis: 129,143 (controls: 496,666); Severe psoriasis: 3603 (controls 14,330)	Hazard ratio: Mild psoriasis: 1.06 (95% CI 1.0–1.1); Severe psoriasis: 1.43 (95% CI 1.1–1.9)	United Kingdom/Cohort study
Kaye et al., 2008 [8]	Myocardial infarction Stroke	Psoriasis: 44,164; Controls: 219,784	Hazard ratio: Myocardial infarction: 1.21 (95% CI 1.10–1.32); Stroke: 1.12 (95% CI 1.00–1.25)	United Kingdom/Cohort study
Lai et al., 2016 [27]	Myocardial infarction Ischemic heart disease Stroke	Psoriasis: 520; Total subjects: 19,065	Odds ratio: Myocardial infarction: 2.24 (95% CI 1.27–3.95); Ischemic heart disease: 1.90 (95% CI 1.18–3.05); Stroke: 1.01 (95% CI 0.48–2.16)	United States/ Cross-sectional study
Lan et al., 2012 [48]	Cerebrovascular disease	Psoriasis: 8180; Controls: 163,600	Hazard ratio: 1.28 (95% CI 1.162–1.413)	Taiwan/Retrospective cohort study
Levesque et al., 2013 [29]	Myocardial infarction	Psoriasis: 31,421; Controls: 31,421	Hazard ratio: 1.17 (95% CI 1.04–1.31)	Canada/Retrospective cohort study
Li et al., 2012 [28]	Nonfatal cardiovascular disease (nonfatal myocardial infarction, nonfatal stroke)	Participants: 96,008 (women); Psoriasis: 2463	Hazard ratio: Myocardial infarction: 1.70 (95% CI 1.01–2.86); Stroke: 1.45 (95% CI 0.80–2.65)	United States/Cohort study
Lin et al., 2011 [30]	Myocardial infarction	Psoriasis: 4752; Controls: 23,760	Hazard ratio: 2.10 (95% CI 1.27–3.43)	Taiwan/Retrospective cohort study
Mallbris et al., 2004 [49]	Cardiovascular mortality	Psoriasis inpatients: 8991; Psoriasis outpatients: 19,757	Standardized mortality ratio: Inpatients: 1.52 (95% CI 1.44–1.60); Outpatients: 0.94 (95% CI 0.89–0.99)	Sweden/Cohort study
Mehta et al., 2010 [18]	Cardiovascular mortality	Severe psoriasis: 3603; Controls: 14,330	Hazard ratio: 1.57 (95% CI 1.26–1.96)	United Kingdom/Cohort study
Ogdie et al., 2015 [25]	Major adverse cardiovascular events (including myocardial infarction, cerebrovascular accidents and cardiovascular death)	Psoriasis: 138,424; Controls: 81,573	Hazard ratio: Mild psoriasis (no DMARD): 1.08 (95% CI 1.02–1.15); Severe psoriasis (DMARD user): 1.42 (95% CI 1.17–1.73)	United Kingdom/Cohort study

Table 1. Cont.

Study	Cardiovascular Comorbidities	Number of Patients/Controls	Relative Risk	Population/Type of Study
Prodanovich et al., 2009 [42]	Ischemic heart disease; Cerebrovascular disease; Peripheral vascular disease	Psoriasis: 3236; Controls: 2500	Odds ratio: Ischemic heart disease: 1.78 (95% CI 1.51–2.11); Cerebrovascular disease: 1.70 (95% CI 1.33–2.17); Peripheral vascular disease: 1.98 (95% CI 1.38–2.82)	United States/Observational cross-sectional study
Shiba et al., 2016 [31]	Coronary heart disease	Hospital-based population: 113,065; Psoriasis: 1197	Odds ratio: 1.27 (95% CI 1.01–1.58)	Japan/Cross-sectional study
Stern et al., 2011 [33]	Cardiovascular mortality	Severe psoriasis: 1376	Standard mortality ratio: 1.02 (95% CI 0.90–1.16)	United States/Prospective cohort study
Wakkee et al., 2010 [34]	Ischemic heart disease hospitalization	Psoriasis: 15,820; Controls: 27,577	Hazard ratio: 1.05 (95% CI 0.95–1.17)	Netherlands/Cohort study
Wu et al., 2015 [26]	Myocardial infarction	Mild psoriasis: 10,173 (controls: 50,865); Severe psoriasis: 3841 (controls: 19,205)	Hazard ratio: Mild psoriasis: 1.31 (95% CI 1.14–1.51); Severe psoriasis: 1.28 (95% CI 1.02–1.60)	United States/Retrospective cohort study

CI = confidence interval.

We have previously performed a population-based study using information from the Taiwanese National Health Insurance Database. The study involved 8180 patients with psoriasis and 163,600 controls. The time relationship between the development of psoriasis and metabolic disorders (hypertension, diabetes or dyslipidemia) was investigated. Psoriasis was regarded as the initiator of the systemic inflammatory march if the metabolic disorder appeared after the diagnosis of psoriasis. On the other hand, psoriasis was regarded as the amplifier of the inflammatory march if the metabolic disorder appeared before the diagnosis of psoriasis. It was found that the risk of developing severe vascular events is higher when psoriasis acts as the disease amplifier compared to when it acts as the disease initiator. In addition, when psoriasis acts as the disease amplifier, methotrexate therapy was associated with a lower risk of developing cerebrovascular disease [50].

In addition, the presence of concomitant psychological disorders may also increase the risk of cardiovascular disease in psoriasis patients. A population-based cohort study in Taiwan found that the risks of ischemic heart disease and stroke are higher in psoriasis patients with sleep disorders compared to psoriasis patients without sleep disorders [51]. In addition, it is known that the psoriasis patients have a higher prevalence of depression [52,53], and the presence of depression has been shown to further increase the risk of myocardial infarction, stroke and cardiovascular mortality in patients with psoriasis [54].

We have also previously performed a nationwide population-based study using the Taiwanese National Health Insurance Database to explore the effect of anxiety on the risk of developing cerebrovascular disease in patients with psoriasis. Our results showed that the prevalence of anxiety disorder is higher in patients with psoriasis compared to non-psoriatic controls, and psoriasis patients with anxiety have a higher risk of developing cerebrovascular disease compared to psoriasis patients without anxiety (hazard ratio 1.37) [55].

3. Psoriasis and Atherosclerosis

A number of studies have attempted to determine the causal relationship between psoriasis and cardiovascular disease. Atherosclerosis is the major pathological change preceding the development of myocardial infarction and stroke. Patients with psoriasis have been found to have increased arterial stiffness compared to healthy controls, and there is a positive correlation between arterial stiffness and psoriasis disease duration [56,57]. Atherosclerosis may also develop following chronic vascular inflammation. Using positron emission tomography/computed tomography (PET/CT), it has been found that patients with psoriasis have greater aortic vascular inflammation, and there is an association between the severity of psoriasis and the degree of vascular inflammation [58]. In addition, it has been shown that improvement of psoriasis skin disease can lead to a reduction of aortic vascular inflammation [59].

Coronary artery atherosclerosis is an important risk factor for ischemic heart disease. Various studies have found that patients with psoriasis have increased prevalence and severity of coronary artery calcification and atherosclerosis (measured by cardiac computed tomography, coronary computed tomography angiography, or coronary angiography) compared to healthy controls [60–66]. Moreover, a reduction in psoriasis disease severity has been found to be associated with an improvement in coronary atherosclerosis [67]. The development of coronary atherosclerosis in psoriasis patients may be partially related to impaired cholesterol efflux capacity from macrophages [68,69].

Atherosclerosis of the carotid artery is recognized as a risk factor for the development of cerebrovascular disease. Using carotid artery ultrasound, various studies have found that patients with psoriasis have greater carotid intima-media thickness compared to healthy controls, indicating carotid atherosclerosis [70–74]. The severity of skin disease (measured by Psoriasis Area and Severity Index (PASI) score) has been found to correlate with carotid intima-media thickness values [75]. A recent meta-analysis of 20 studies also confirmed that patients with psoriasis have greater carotid intima-media thickness values and decreased flow-mediated dilation compared to healthy controls, thus demonstrating an association between psoriasis and subclinical carotid atherosclerosis [76].

In addition, epicardial fat tissue has been shown to be a cardiovascular risk factor and is associated with the development of atherosclerosis. The epicardial fat thickness or area (measured by transthoracic echocardiography or computed tomography) has been found to be greater in patients with psoriasis compared to healthy controls [77–80]. This may contribute to the greater cardiovascular risk in patients with psoriasis [81].

4. Psoriasis and Cardiovascular Risk Factors

Various studies have found that psoriasis is associated with greater prevalence of cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, obesity, and the metabolic syndrome [8,10]. These cardiovascular risk factors will be discussed in more detail below.

4.1. Hypertension

A number of studies have shown significant associations between psoriasis and the prevalence of hypertension [8,43,82–85]. A meta-analysis found increased prevalence of hypertension in psoriasis patients, with odds ratios of 1.30 for mild psoriasis and 1.49 for severe psoriasis [86]. Patients with psoriasis were also found to have higher risk of uncontrolled hypertension, and the risk correlates with psoriasis disease severity [15].

In addition, the presence of hypertension may increase the risk of incident psoriasis. In the Nurses' Health Study involving 77,728 women, patients with hypertension were found to have a higher risk of developing psoriasis [87]. This may be associated with the use of beta-blockers to treat hypertension.

4.2. Diabetes Mellitus

A number of studies have found that the prevalence rate of diabetes mellitus is higher in patients with psoriasis [8,43,85,88,89]. According to a previous meta-analysis, psoriasis is associated with a greater risk of diabetes mellitus with odds ratios of 1.53 for mild psoriasis and 1.97 for severe psoriasis [90]. In a population-based cohort study from Taiwan, it was found that psoriasis is associated with the development of diabetes, and the risk is greater for severe disease (hazard ratio 2.06) compared to mild disease (hazard ratio 1.28) [91]. Patients with psoriasis have also been found to have greater insulin resistance compared to normal controls, suggesting that psoriasis may be a prediabetic disorder [92]. In patients with psoriasis associated with diabetes, glycemic control with hypoglycemic medications has been shown to improve the skin condition [93].

Metformin is known as an insulin sensitizer and has been demonstrated to prevent the development of diabetes, promote weight loss, and reduce the incidence of metabolic syndrome, which may lead to a more favorable cardiovascular risk profile [94–98]. Previously, treatment of psoriasis patients with metabolic disorders with metformin has been demonstrated to decrease psoriasis severity and improve the parameters of the metabolic syndrome [99,100]. In patients with diabetes, treatment with thiazolidinediones and metformin has also been shown to reduce the risk of developing psoriasis [101,102], while regular insulin use may increase psoriasis risk [102].

The risk of diabetic complications in patients with psoriasis has also been investigated. Patients with concomitant diabetes and psoriasis have been shown to have greater risk of developing microvascular and macrovascular complications, compared to diabetic patients without psoriasis [103]. Patients with severe psoriasis have also been found to have greater levels of advanced glycation end products in their blood and skin [104].

4.3. Dyslipidemia

A number of studies have demonstrated a higher prevalence of dyslipidemia in patients with psoriasis [9,10,43,105–107]. Patients with psoriasis have been found to have increased risk of hypercholesterolemia [108–110]. In addition, a number of studies have shown that psoriasis is associated with decreased high-density lipoprotein (HDL) level and increased low-density lipoprotein

(LDL) level [107,110–112]. Abnormalities in lipoprotein profile have also been found in pediatric patients with psoriasis [113].

Apart from blood cholesterol abnormalities, serum triglyceride levels have also been found to be increased in patients with psoriasis compared to healthy controls [107,110]. In addition, serum fatty acid profile was found to be abnormal in patients with psoriasis compared to healthy controls [114].

Some studies have also shown that dyslipidemia may precede the development of psoriasis. The Nurses' Health Study II showed that patients with hypercholesterolemia have increased risk of developing psoriasis (hazard ratio 1.25), and the risk is greater for patients with longer duration of hypercholesterolemia (more than 7 years) [115]. Therefore, the temporal relationship between psoriasis and dyslipidemia requires further investigation.

4.4. Obesity

It is known that psoriasis is associated with increased prevalence of obesity [43,106,110,116,117], particularly central obesity (as measured by waist-to-height ratio or waist circumference) [118,119]. In a cross-sectional survey performed in Germany, the mean body mass index (BMI) of patients with psoriasis (28.0) was shown to be significantly higher than normal controls (25.9) [120]. The severity of psoriatic skin disease had also been shown to correlate with the degree of obesity (determined by BMI or waist-to-height ratio) [118,121]. The association between psoriasis and obesity (particularly central adiposity) has also been found in the pediatric population [122–125].

The temporal relationship between psoriasis and obesity is currently not completely defined. Various studies have indicated that obesity may be a risk factor for developing psoriasis [126]. A previous large-scale prospective study found that increased BMI is associated with greater incidence of psoriasis, which indicates that obesity occurs before the development of psoriasis [116]. In addition, a dose-response relationship was found between the degree of obesity (BMI) and the risk of developing psoriasis [116,127]. On the other hand, another study demonstrated that obesity occurred after the onset of psoriasis, suggesting that obesity is a consequence and not a risk factor for psoriasis [128].

Various studies have also shown that in psoriasis patients with obesity, weight loss (including dietary measures, physical exercise or surgical gastrectomy) can lead to improvement of the skin condition [129–134]. In patients with psoriasis who were obese, weight loss has also been shown to increase the efficacy of anti-TNF- α biologic therapy [135].

The molecular mechanisms underlying the association between psoriasis and obesity are currently not clearly understood. Various studies have shown that the disordered production of adipokines from fat tissue in obese patients with psoriasis may lead to chronic skin and systemic inflammation and increased cardiovascular risk [136,137].

4.5. Metabolic Syndrome

Components of the metabolic syndrome include hyperglycemia, central/abdominal obesity, hypertension, and dyslipidemia (hypertriglyceridemia or low HDL level) [138,139]. Various studies have shown that psoriasis is associated with an increased prevalence of the metabolic syndrome [43,106,140–143]. Moreover, the frequency of the metabolic syndrome was found to increase with greater psoriasis disease severity [14,144,145]. An association between psoriasis and metabolic syndrome has also been found in the Asian population, including Thailand [146], China [147], and India [148]. In addition, children with psoriasis were shown to have a higher prevalence of the metabolic syndrome [124,149].

4.6. Cigarette Smoking and Alcohol Consumption

Both cigarette smoking and alcohol use are known cardiovascular risk factors. Various studies have shown increased prevalence of cigarette smoking and alcohol consumption in patients with psoriasis [128,150–157]. A recent meta-analysis also demonstrated a significant association between smoking and psoriasis disease severity [158]. However, it is not clearly defined whether cigarette

smoking and alcohol consumption may increase the risk of developing psoriasis, or whether they occur as a consequence of psoriasis-associated psychological stress. A previous meta-analysis indicated that cigarette smoking predates psoriasis and may be an independent risk factor for psoriasis development [152]. Mechanistically, previous studies have demonstrated increased amount of peripheral blood Th17 cells in psoriasis patients who smoke [159], which may partially explain the increased risk of psoriasis in cigarette smokers.

5. Relationship between Severity of Psoriasis (in Terms of PASI and BSA) and Cardiovascular Risk

Some of the studies showing an association between the severity of psoriasis and the risk of cardiovascular comorbidities have used the PASI score as a measure of psoriasis severity [58,59,67,118,144,160–162]. On the other hand, some studies have shown an association between BSA involvement and cardiovascular risk [14,15,125,163,164]. Currently, it is not known whether PASI or BSA correlate better with cardiovascular risk in patients with psoriasis. In addition, at present there is no specific PASI/BSA threshold above which systemic therapy is recommended due to increased risk of cardiovascular comorbidities. Although patients with palmoplantar or pustular psoriasis may have low PASI/BSA scores, they may have significant systemic inflammation. A few small-scale studies have shown an association between palmoplantar/nail and pustular forms of psoriasis and cardiovascular comorbidities [165,166], although this is contradicted by another study [167].

6. Psoriatic Arthritis and Cardiovascular Comorbidities

A number of studies have demonstrated that psoriatic arthritis is associated with higher prevalence of cardiovascular and metabolic diseases. In particular, there is a greater risk of developing severe vascular events such as myocardial infarction and stroke [25,168–171]. Patients with psoriatic arthritis have also been found to have higher risk of atherosclerosis [172,173]. In addition, the prevalence of cardiovascular risk factors are increased in patients with psoriatic arthritis, including hypertension, diabetes, obesity, dyslipidemia, and metabolic syndrome [174–178].

We have previously carried out a retrospective cohort study using the Taiwanese National Health Insurance Database. In total, 284 psoriasis patients with arthritis and 7648 psoriasis patients without arthritis were included. It was found that psoriasis patients with arthritis had a higher risk of developing severe vascular events (hazard ratio 1.46 for cardiovascular disease and 1.82 for cerebrovascular disease), compared to psoriasis patients without arthritis [179].

7. Pathogenic Mechanisms

Various studies have attempted to define the molecular mechanisms responsible for the association between psoriasis and cardiovascular comorbidities. Mechanisms which have been proposed include shared genetic factors, common inflammatory pathways, secretion of adipokines, insulin resistance, lipoprotein composition and function, angiogenesis, oxidative stress, microparticles, and hypercoagulability.

7.1. Shared Genetic Factors

One particular question is whether there is a genetic basis for the increased prevalence of cardiovascular comorbidities in psoriasis patients. Genome-wide association studies have found increased inheritance of certain genes that are associated with cardiovascular risk in patients with psoriasis, indicating shared genetic factors [180]. Other shared genetic factors between psoriasis and cardiometabolic diseases that have been found include CDKAL1, apolipoprotein E, and interleukins [181–183]. However, a number of studies have shown that psoriasis and cardiometabolic disorders do not share common genetic risk loci [184,185].

7.2. Common Inflammatory Pathways

The association between psoriasis and cardiovascular disease may be partly explained by common inflammatory pathways [186,187]. Chronic skin inflammation may lead to vascular and systemic inflammation, atherosclerosis, and thrombosis. Patients with psoriasis have been shown to have increased vascular, subcutaneous and hepatic inflammation (assessed by PET/CT scan) compared to healthy controls [188–191]. Animal studies have also shown that chronic skin inflammation may induce vascular inflammation [192]. Moreover, the systemic inflammatory marker C-reactive protein (CRP) has been found to be elevated in patients with psoriasis [193,194]. Furthermore, a previous meta-analysis of 5 microarray data sets found that psoriasis lesional skin shows increased expression of genes associated with atherosclerosis signaling and fatty acid metabolism [195].

The cytokine profiles of psoriasis skin lesions and atherosclerosis vascular lesions are very similar, showing increased number of Th1 and Th17 lymphocytes [186,196,197]. The Th1 and Th17 cytokine pathways have been shown to be involved in the pathogenesis of both psoriasis and atherosclerosis [197–202]. Similar to psoriasis, patients with ischemic heart disease have increased levels of Th17-related cytokines (IL-17, IL-6 and IL-8) in their peripheral blood [203]. Therefore, the overexpression of Th17 cytokines in patients with psoriasis may mediate vascular inflammation and the development of atherosclerosis and cardiovascular comorbidities [204,205]. In addition, the skin lesions and blood of psoriasis patients have been shown to contain increased levels of cardiovascular biomarkers, including monocyte chemoattractant protein-1 and macrophage-derived chemokine [206].

However, the temporal relationship between psoriatic systemic inflammation and cardiovascular disease remains unclear. It is possible that the systemic inflammation of psoriasis may lead to the development of cardiovascular diseases, or alternatively the cardiovascular risk factors may cause immune dysfunction leading to psoriasis. In the theory known as the “psoriatic march”, it is proposed that psoriasis may induce systemic inflammation leading to insulin resistance, endothelial dysfunction, and development of atherosclerosis and cardiovascular comorbidities [196,207].

7.3. Adipokines

The systemic inflammation associated with psoriasis may lead to inflammation of the adipose tissue, which may promote the release of pro-inflammatory adipokines into the peripheral blood. A number of studies have shown that adipokines (including leptin, adiponectin and resistin) may be involved in the development of the metabolic syndrome and cardiovascular comorbidities [208].

Leptin is known as a pro-inflammatory adipokine. Previously, serum leptin levels have been shown to be elevated in psoriasis patients and correlate with psoriasis disease severity [209–211]. Moreover, increased leptin expression may induce increased levels of pro-inflammatory cytokines leading to exacerbation of psoriasis [137,212]. In patients with psoriasis, increased leptin expression has been shown to be associated with the metabolic syndrome [209,213]. Serum leptin level has also been found to correlate with subclinical atherosclerosis (carotid intima-media wall thickness) in psoriasis patients [214]. On the other hand, adiponectin is an anti-inflammatory adipokine. Previous studies have found decreased serum levels of adiponectin in psoriasis patients [211,215], which may contribute to the systemic inflammation of psoriasis. In addition, resistin and visfatin are pro-inflammatory adipokines. Serum levels of resistin and visfatin have been found to be increased in psoriasis patients and correlate with disease severity [214,216,217].

7.4. Insulin Resistance

It has been shown that patients with psoriasis have greater insulin resistance compared to normal controls [92]. The development of insulin resistance in psoriasis patients may provide a mechanistic explanation for the increased risk of atherosclerosis and cardiovascular comorbidities.

7.5. Lipoprotein Composition and Function

The composition and function of lipoprotein particles may be altered in psoriasis patients. Previous studies have shown that the antioxidant and anti-inflammatory activities of HDL are reduced in patients with psoriasis compared to healthy controls, indicating functional impairment of HDL in psoriasis [218]. In patients with psoriasis, changes in the composition of HDL particles may also impede their capacity to induce cholesterol efflux from macrophages, thus leading to atherosclerosis and cardiovascular disease [68,69]. Interestingly, both the HDL particle composition and cholesterol efflux ability become normalized following anti-psoriasis therapy [219].

7.6. Angiogenesis and Oxidative Stress

Both psoriasis skin lesions and atherosclerotic plaques are characterized by increased angiogenesis [220–222]. The production of pro-angiogenic factors (including vascular endothelial growth factor and interleukin-8) from psoriasis plaques may lead to the development and progression of atherosclerosis [223,224]. In addition, common oxidative stress signaling pathways may underlie the association between psoriasis and atherosclerosis [223,225,226].

7.7. Microparticles

Microparticles are composed of plasma membrane vesicles which may be derived from endothelial cells, platelets and monocytes/macrophages. They contain nucleic acids and various inflammatory mediators [7]. They may be released as a result of cell activation or apoptosis, and are involved in the development of atherosclerosis [227]. Previous studies have shown that psoriasis patients have increased blood levels of microparticles, which may contribute to the development of atherosclerosis and cardiovascular comorbidities [228–230].

7.8. Hypercoagulability

Patients with psoriasis have been shown to exhibit increased platelet activation and aggregation [229,231,232]. Moreover, psoriasis patients may have increased blood levels of plasminogen activator inhibitor-1 [233]. These factors may lead to a hypercoagulable state and increased risk of thromboembolic events in patients with psoriasis.

7.9. Serum Homocysteine Level

Homocysteine induces oxidative stress, and elevated plasma homocysteine level has been found to be associated with the development of atherosclerosis and cardiovascular diseases [234,235]. Previous studies have shown that plasma homocysteine levels are elevated and folate levels decreased in patients with psoriasis, and correlate with psoriasis disease severity [236]. This may contribute to the formation of atherosclerotic plaques in psoriasis patients.

8. Biomarkers of Systemic Inflammation

Although there appears to be an association between psoriasis severity and the risk of cardiovascular diseases, the severity of skin disease may not closely correlate with the degree of vascular or systemic inflammation. Patients with psoriatic arthritis may show only mild skin disease, but may have severe systemic inflammation. Therefore, identification of serum biomarkers of systemic inflammation is important for assessing cardiovascular risk [7].

Psoriasis patients have been found to have altered levels of traditional cardiovascular biomarkers, including CRP, soluble CD40 ligand, human matrix Gla protein and fetuin-A [194,237–239]. Other proposed biomarkers of inflammation and cardiovascular risk in psoriasis include serum YKL-40 [240], GlycA [241], and complement C3 [242]. The peripheral blood neutrophil/lymphocyte ratio has also been found to be elevated in psoriasis patients and may act as a marker of subclinical

atherosclerosis [243,244]. In addition, serum myeloperoxidase (MPO) level is elevated in psoriasis and may be a biomarker for cardiovascular risk [245].

9. Effects of Anti-Psoriasis Therapies on Cardiovascular Comorbidities

Adequate treatment of psoriasis patients, particularly those with moderate to severe disease, may decrease the risk of cardiovascular comorbidities. This may occur as a result of suppression of systemic inflammation. Systemic forms of treatment for psoriasis include ultraviolet light phototherapy, immunosuppressive agents (methotrexate, cyclosporine), oral retinoid (acitretin), fumaric acid esters, and biological agents (TNF- α inhibitors) [246,247]. Various treatment modalities for psoriasis may have different impacts on the cardiovascular system. A number of studies have shown that phototherapy does not have a significant impact on the risk of cardiovascular events [248–250]. Systemic treatments for psoriasis and their effects on cardiovascular risk are discussed below. The findings from studies investigating the effects of different psoriasis treatments on the risk of cardiovascular disease in patients with psoriasis are summarized in Table 2.

9.1. Methotrexate

A number of studies have demonstrated that treatment of psoriasis patients with methotrexate may decrease the risk of cardiovascular events (including ischemic heart disease, stroke, and cardiovascular death) [248,250–254]. In particular, low-dose methotrexate has been found to be effective in decreasing the risk of cardiovascular diseases in patients with psoriasis [251].

We have previously performed a population-based study utilizing the Taiwanese National Health Insurance Database. A total of 8180 patients with psoriasis and 163,600 patients without psoriasis were included. It was found that psoriasis is associated with greater risk of cerebrovascular disease (hazard ratio 1.28 compared to non-psoriasis patients). This risk was significantly reduced with methotrexate treatment (hazard ratio 0.50) but not retinoid treatment. In addition, this protective effect was only seen with low cumulative methotrexate dose but not high cumulative dose [48]. Therefore, low-dose methotrexate treatment is effective in preventing the occurrence of cerebrovascular disease in psoriasis patients. In addition, we have previously found that methotrexate treatment was associated with lower risk of cardiovascular disease in psoriasis patients without arthritis [179].

9.2. Cyclosporine

In a subset of patients with psoriasis, treatment with cyclosporine may lead to impaired renal function, hypertension and increased cardiovascular risk. In addition, hyperlipidemia may occur in psoriasis patients treated with cyclosporine. Therefore, it is recommended that in patients with psoriasis, cyclosporine should only be used for a limited duration, and another systemic agent should be substituted once the skin condition is improved [7]. A previous study has shown that treatment of patients with severe psoriasis with cyclosporine does not have a protective effect on the development of cardiovascular events (myocardial infarction, stroke, cardiovascular death) [252].

9.3. Acitretin

Acitretin is most commonly used to treat generalized pustular psoriasis. In a subset of patients, acitretin may cause hyperlipidemia, which should be actively treated to avoid increased cardiovascular risk. Previous studies in humans and animals have shown that retinoids may improve and ameliorate the formation of atherosclerotic plaques [255–261]. Further investigations are required to determine whether treatment of psoriasis patients with retinoids may prevent the development of atherosclerosis and decrease the risk of cardiovascular events.

Table 2. Studies investigating the effects of different psoriasis treatments on the risk of cardiovascular disease in patients with psoriasis.

Study	Treatment for Psoriasis	Cardiovascular Endpoint	Number of Patients	Relative Risk	Population/Type of Study
Abuabara et al., 2011 [262]	Systemic immunomodulatory therapies (methotrexate, cyclosporine, alefacept, efalizumab, adalimumab, etanercept, infliximab)	Myocardial infarction	Psoriasis: 25,554; Phototherapy: 4220; Systemic treatment: 20,094; Both treatments: 1240	Hazard ratio (compared to UVB phototherapy): 1.33 (95% CI 0.90–1.96)	United States/Cohort study
Ahlehoff et al., 2013 [254]	Biological agents; Methotrexate	Cardiovascular death, myocardial infarction and stroke	Severe psoriasis: 2400; Biological agents: 693; Methotrexate: 799; Other therapies: 908	Hazard ratio (compared to other therapies): Biological agents: 0.48 (95% CI 0.17–1.38); Methotrexate: 0.50 (95% CI 0.26–0.97)	Denmark/Retrospective cohort study
Ahlehoff et al., 2015 [252]	Methotrexate; Cyclosporine; Retinoids; TNF- α inhibitors; Ustekinumab	Cardiovascular events (cardiovascular death, myocardial infarction, stroke)	Severe psoriasis: 6902; Methotrexate: 3564; Cyclosporine: 244; Retinoids: 756; TNF- α inhibitors: 959; Ustekinumab: 178	Hazard ratio (compared to other therapies): Methotrexate: 0.53 (95% CI 0.34–0.83); Cyclosporine: 1.06 (95% CI 0.26–4.27); Retinoids: 1.80 (95% CI 1.03–2.96); TNF- α inhibitors: 0.46 (95% CI 0.22–0.98); Ustekinumab: 1.52 (95% CI 0.47–4.94)	Denmark/Cohort study
Chin et al., 2013 [179]	Methotrexate; Retinoid	Cardiovascular disease; Cerebrovascular disease	Psoriasis patients without arthritis: 7648	Hazard ratio (compared to no methotrexate and no retinoid treatment): Cardiovascular disease: Methotrexate: 0.39 (95% CI 0.20–0.76); Retinoid 0.47 (95% CI 0.26–0.83); Cerebrovascular disease: Methotrexate: 0.42 (95% CI 0.19–0.95); Retinoid: 0.67 (95% CI 0.35–1.31)	Taiwan/Retrospective cohort study
Lan et al., 2012 [48]	Methotrexate; Retinoid	Cerebrovascular disease	Psoriasis: 8180; Methotrexate: 258; Retinoid: 193	Hazard ratio (compared to no methotrexate and no retinoid treatment): Methotrexate: 0.50 (95% CI 0.27–0.92); Retinoid: 0.70 (95% CI 0.39–1.23)	Taiwan/Retrospective cohort study
Prodanovich et al., 2005 [251]	Methotrexate	Vascular disease (including cardiovascular disease, cerebrovascular disease, atherosclerosis)	Psoriasis: 7615	Relative risk (compared to no methotrexate treatment): Methotrexate: 0.73 (95% CI 0.55–0.98); Low cumulative dose methotrexate: 0.50 (95% CI 0.31–0.79)	United States/Retrospective cohort study

Table 2. Cont.

Study	Treatment for Psoriasis	Cardiovascular Endpoint	Number of Patients	Relative Risk	Population/Type of Study
Wu et al., 2012 [263]	TNF inhibitor	Myocardial infarction	Psoriasis: 8845; TNF inhibitor: 1673	Hazard ratio (compared to topical therapy): TNF inhibitor: 0.50 (95% CI 0.32–0.79)	United States/Retrospective cohort study
Wu et al., 2013 [264]	TNF inhibitor; Oral/phototherapy	Myocardial infarction	Psoriasis: 8845; Caucasians: 4645 (TNF inhibitor: 857; Oral/phototherapy: 1011; Topical: 2777); Non-Caucasians: 4200 (TNF inhibitor: 816; Oral/phototherapy: 1086; Topical: 2298)	Hazard ratio (compared to topical therapy): Caucasians: TNF inhibitors: 0.35 (95% CI 0.20–0.62); Oral/phototherapy: 0.36 (95% CI 0.22–0.59); Non-Caucasians: TNF inhibitors: 0.27 (95% CI 0.11–0.67); Oral/phototherapy: 0.58 (95% CI 0.32–1.04)	United States/Retrospective cohort study
Wu et al., 2013 [265]	TNF inhibitor (etanercept or monoclonal antibody)	Myocardial infarction	Etanercept: 976; Monoclonal antibody: 217; Topical therapy: 5075	Hazard ratio (compared to topical agents): Etanercept: 0.53 (95% CI 0.31–0.92); Monoclonal antibody: 0.25 (95% CI 0.06–1.03)	United States/Retrospective cohort study
Wu et al., 2014 [266]	TNF inhibitor	Myocardial infarction	Psoriasis (treated with TNF inhibitor): 846; Psoriasis (not treated with TNF inhibitor): 7172	Hazard ratio (compared to psoriasis patients not treated with TNF inhibitors): 0.26 (95% CI 0.12–0.56)	United States/Retrospective cohort study
Wu et al., 2017 [267]	TNF inhibitor	Major cardiovascular events (myocardial infarction, stroke or transient ischemic attack, unstable angina)	TNF inhibitor: 9148; Methotrexate: 8581	Hazard ratio (compared to methotrexate): Major cardiovascular event: 0.55 (95% CI 0.45–0.67) Myocardial infarction: 0.49 (95% CI 0.34–0.71); Stroke or TIA: 0.55 (95% CI 0.42–0.71); Unstable angina: 0.58 (95% CI 0.41–0.82)	United States/Retrospective cohort study

CI = confidence interval.

9.4. Fumaric Acid Esters

Fumaric acid esters have been widely used in Germany to treat psoriasis. Treatment with fumaric acid esters have been shown to decrease serum CRP level and increase adiponectin level (a cardioprotective adipokine) in patients with psoriasis [268,269]. Further investigations are required to determine whether this form of treatment may reduce cardiovascular risk.

9.5. Tumor Necrosis Factor-Alpha (TNF- α) Inhibitors

Various studies have shown that treatment of psoriasis patients with TNF- α inhibitors may lower the risk of cardiovascular comorbidities. Compared to patients who received topical therapy, psoriasis patients treated with TNF- α inhibitors showed a significant decrease in the risk of myocardial infarction (hazard ratio 0.50) [263]. Other studies have also confirmed the beneficial effects of TNF- α inhibitors in reducing the risk of myocardial infarction in psoriasis patients [264–266,270–272]. In addition, a number of studies have shown that treatment of psoriasis patients with TNF- α inhibitors leads to decreased risk of cardiovascular events compared to methotrexate, and greater risk reduction was found with longer duration of anti-TNF- α treatment [267,273].

Treatment of psoriasis patients with TNF- α inhibitors may also have beneficial effects on the development of atherosclerosis and components of the metabolic syndrome. Anti-TNF- α therapy in patients with severe psoriasis has been shown to improve subclinical cardiovascular disease (abnormalities in echocardiogram) [13], improve coronary microvascular function (determined by transthoracic Doppler echocardiography) [274], and attenuate the progression in coronary artery disease (assessed by coronary computed tomography) [275]. Treatment of patients with moderate to severe psoriasis with adalimumab for 6 months led to improvement in endothelial function (brachial artery reactivity) and carotid arterial stiffness [276]. However, another study found that treatment of patients with psoriasis with adalimumab for 16 weeks had no significant effect on vascular inflammation (determined by PET/CT scan) in the carotid arteries or aorta [277]. In addition, TNF- α inhibitor treatment may decrease the risk of diabetes mellitus in patients with psoriasis [278], and improve insulin sensitivity both in diabetic [279] and non-diabetic patients [280]. However, another study found that combination anti-TNF- α and methotrexate treatment did not improve hemoglobin A_{1C} and fasting glucose level compared to methotrexate treatment alone [281].

On the other hand, a number of studies have shown that treatment with TNF- α inhibitors may lead to increased body weight and BMI in patients with psoriasis [282–284]. Therefore, body weight should be monitored in psoriasis patients treated with TNF- α inhibitors, and appropriate weight reduction measures may be required to reduce the cardiovascular risk.

Furthermore, treatment of psoriasis patients with TNF- α inhibitors may improve biomarkers of cardiovascular risk. Patients with psoriasis who were treated with etanercept showed decreased blood levels of cardiovascular biomarkers, such as soluble VCAM-1, soluble ICAM-1, soluble E-selectin, MMP-9, MPO, and tPAI-1 [249]. Psoriasis patients who received adalimumab also showed decreased serum levels of cardiovascular biomarkers E-selectin and IL-22 [285,286]. Other studies demonstrated that treatment of psoriasis patients with etanercept led to decreased CRP levels [287,288]. Treatment of psoriasis patients with TNF- α inhibitors has been shown to suppress serum leptin levels [289]. Furthermore, patients with psoriasis who received anti-TNF- α agents showed decreased amount of peripheral blood endothelial and platelet microparticles [290].

9.6. Anti-IL-12/23 Agents

Two meta-analysis studies have suggested that short-term treatment of psoriasis patients with anti-IL-12/23 agents (ustekinumab and briakinumab) may be associated with increased risk of major adverse cardiovascular events [291,292]. On the other hand, a long-term study over 5 years indicated that ustekinumab treatment does not increase or decrease the incidence of major adverse cardiovascular events in patients with psoriasis [293]. Other studies have also shown that treatment of

psoriasis patients with ustekinumab does not lead to increased risk of major adverse cardiovascular events [248,250,294,295].

A recent study showed that ustekinumab may improve coronary and myocardial function in psoriasis patients [296], while another study revealed that it may increase fasting sugar and triglyceride levels [297]. Further investigations are required to confirm whether ustekinumab may have beneficial or detrimental effects on the cardiovascular system in the long term.

9.7. Anti-IL-17 Agents

Anti-IL-17 agents (such as secukinumab) have recently been used for the treatment of psoriasis. Patients with psoriasis treated with anti-IL-17 agents have shown no increased incidence of major adverse cardiovascular events [298,299]. However, further long-term studies are needed to evaluate whether anti-IL-17 agents may have beneficial effects on cardiovascular comorbidities in patients with psoriasis [300].

9.8. Apremilast

Apremilast is an oral phosphodiesterase-4 inhibitor which has recently been approved for the treatment of psoriasis [301]. In randomized controlled trials, patients with psoriasis receiving apremilast have shown no increased risk of major cardiac events up to 156 weeks [302,303]. Further long-term large-scale studies are required to determine whether this relatively new drug may have beneficial effects on cardiovascular risk in psoriasis.

10. Conclusions

Recent studies have shown that psoriasis is not a disease affecting only the skin and joints, but may be associated with various cardiovascular and metabolic disorders. Patients with psoriasis have been shown to have a higher prevalence of cardiovascular risk factors including hypertension, diabetes, dyslipidemia, obesity, metabolic syndrome and smoking, and are at increased risk of developing severe vascular events (including myocardial infarction and stroke). The presence of common inflammatory pathways may provide an explanation for the association between psoriasis and cardiovascular comorbidities.

Physicians should be more aware of the cardiovascular risk when assessing patients with psoriasis. In particular, adequate treatment of psoriasis may not only ameliorate the skin condition, but also decrease the risk and severity of cardiovascular and metabolic disorders. Further investigations are required to clarify the mechanisms underlying the association between psoriasis and cardiovascular comorbidities, and define optimal treatment regimens to reduce the risk of cardiovascular events in patients with psoriasis.

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Abbreviations

PET/CT	Positron emission tomography/computed tomography
PASI	Psoriasis area and severity index
BSA	Body surface area
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
BMI	Body mass index
CRP	C-Reactive protein
TNF- α	Tumor necrosis factor- α

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