INTERNAL MEDICINE

□ REVIEW ARTICLE □

Cardiovascular and Metabolic Diseases Comorbid with Psoriasis: Beyond the Skin

Masutaka Furue[1], Gaku Tsuji[1], Takahito Chiba[1] and Takafumi Kadono[2]

Abstract

A close association of systemic inflammation with cardiovascular diseases and metabolic syndrome is recently a popular topic in medicine. Psoriasis is a chronic inflammatory skin disease with a prevalence of approximately 0.1-0.5% in Asians. It is characterized by widespread scaly erythematous macules that cause significant physical and psychological burdens for the affected individuals. The accelerated inflammation driven by the TNF-α/IL-23/IL-17A axis is now known to be the major mechanism in the development of psoriasis. Psoriasis is not a mere skin disease; it is significantly associated with cardiovascular diseases and metabolic syndrome, which suggests that the chronic skin inflammation extends the systemic inflammation beyond the skin. In this article, we review the epidemiological and pathological aspects of psoriasis and its comorbidities.

Key words: psoriasis, cardiovascular disease, metabolic syndrome, tumor necrosis factor α, interleukin 23, interleukin 17

(Intern Med 56: 1613-1619, 2017)
(DOI: 10.2169/internalmedicine.56.8209)

Introduction

The close association of systemic inflammation with cardiovascular diseases (CVD) and metabolic syndrome is a recent topic in medicine (1-3). Inflammatory skin diseases such as psoriasis are an integral part of diseases causing systemic inflammation (4). Psoriasis is a common immune-mediated chronic inflammatory skin disease that is characterized by the altered proliferation and differentiation of keratinocytes, vascular remodeling and inflammation in the skin (Figure). Psoriasis shows a diverse prevalence across populations worldwide: 2.5% in Europeans, 0.05-3% in Africans and 0.1-0.5% in Asians (5-8). Psoriasis patients comprise 4.43% of all Japanese dermatological patients (8). Men are likely to experience a higher severity of the disease than women are. Phenotypic heterogeneity of psoriasis has also been reported among ethnic populations. Small plaque psoriasis is specific to Asian populations, while severe psoriasis is more predominant in Western populations (5-8). Recent genome-wide association studies have identified numerous risk-associated variants within 44 susceptibility loci for psoriasis, including *HLA-C*06:02*, *LCE3D*, *IL23R* and *CARD14*. *HLA-C*12:02* may be a susceptibility locus for late-onset psoriasis in the Japanese population (5, 9-11). These susceptibility genes are predominantly related to the innate and adaptive immune systems and skin barrier functions (5, 9).

Pathogenesis of Psoriasis

Like other forms of systemic inflammation, tumor necrosis factor (TNF)-α is a key pro-inflammatory cytokine in psoriasis because its inhibitor significantly improves coronary microvascular dysfunction and levels of highly sensitive C-reactive protein, as well as ameliorates psoriatic symptoms (12). In addition, recent therapeutic success with other biologics seems to have revealed the pivotal role of the TNF-α/interleukin (IL)-23/IL-17 axis in the pathogenesis of psoriasis (Figure). The initial trigger of psoriasis is thought to be the activation of plasmacytoid dendritic cells (DCs) being stimulated by complexes of host DNA and the antimicrobial peptide LL-37 (cathelicidin), which are produced by keratinocytes after minor injuries (8, 13-15). Activated plasmacytoid DCs and damaged keratinocytes produce interferon (IFN)-α and TNF-α, which results in the further

[1]Department of Dermatology, Kyushu University, Japan and [2]Department of Dermatology, St. Marianna University School of Medicine, Japan
Received for publication August 31, 2016; Accepted for publication October 26, 2016
Correspondence to Dr. Masutaka Furue, furue@dermatol.med.kyushu-u.ac.jp

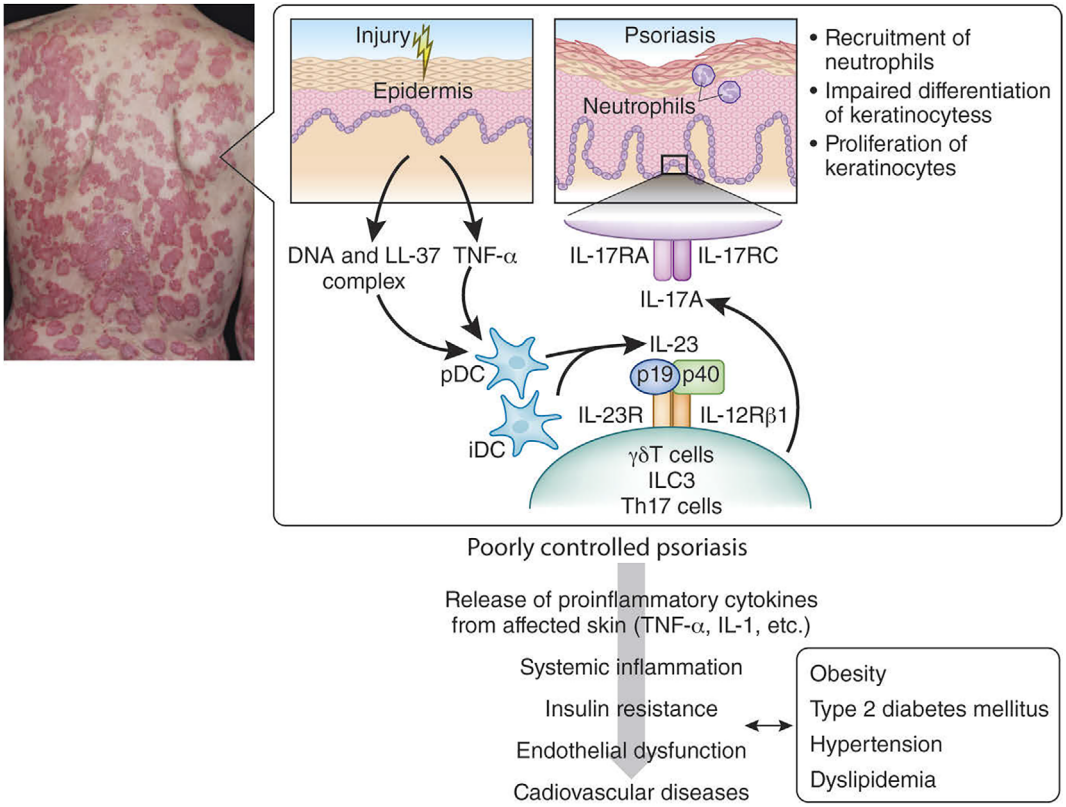

Figure. Pathophysiology of psoriasis and its comorbidities (simplified model modified from references 5, 8 and 67). The initial trigger of psoriasis is thought to be the activation of plasmacytoid dendritic cells (DCs) by complexes of host DNA and the antimicrobial peptide LL-37 (cathelicidin) produced by keratinocytes after minor injuries. Plasmacytoids and recruited inflammatory DCs (pDCs and iDCs) produce TNF-α, IL-12 and IL-23. IL-23 is critically involved in the generation and activation of IL-17-producing effector cells. In humans and experimental psoriasis models, γδT cells (Vγ9Vδ2 T cells in human), innate lymphoid cells type 3 (ILC3) and Th17 cells are detected in the lesional skin and blood, and these cells readily produce IL-17A. IL-17A binds to the IL-17 receptor (IL-17R), which is composed of IL-17RA and IL-17RC. IL-17A upregulates the proliferation and downregulates the differentiation of keratinocytes and also enhances the recruitment of neutrophils and aids in the crosstalk between neutrophils and keratinocytes. Chronically released proinflammatory cytokines (e.g., TNF-α, IL-1) from poorly controlled psoriatic skin to the circulatory system potentiates and perpetuates the systemic inflammation and induces insulin resistance, endothelial dysfunction and cardiovascular diseases. This systemic inflammation also causes obesity, hypertension, dyslipidemia and type 2 diabetes mellitus. These systemic involvements interact with each other to increase the mortality for psoriatic patients from cardiovascular diseases.

production of TNF-α, IL-12 and IL-23 by plasmacytoids and recruited inflammatory DCs (8, 14, 15) (Figure). IL-12 promotes the differentiation of naïve $CD4^+$ T cells into IFN-γ-producing T helper (Th) 1 cells. IL-23 is critically involved in the generation and activation of IL-17-producing effector cells (13, 15, 16) (Figure). In humans and experimental models of psoriasis, γδT cells (Vγ9Vδ2 T cells in human), innate lymphoid cells type 3 (ILC3) and Th17 cells are detected in blood and lesional skin. These cells readily produce IL-17A and IL-22 (8, 17, 18). IL-17A binds to the IL-17 receptor (IL-17R), which is composed of IL-17RA and IL-17RC (19) (Figure). IL-17A upregulates the proliferation of keratinocytes and downregulates its differentiation (20) and also enhances the recruitment of neutrophils and aids in the crosstalk between neutrophils and keratinocytes by upregulating the neutrophil-attractive chemokines CXCL8 and CXCL1 (21). IL-17A promotes the expression of TNF-α by keratinocytes (19), which indicates that the above-mentioned TNF-α/IL-23/IL-17 axis likely forms a vicious loop in the development of psoriasis lesions (Figure). The mechanistic hypothesis coincides with the fact that antibodies against TNF-α, IL-23(p19), IL-23(p40), IL-23R, IL-17A or IL-17RA exert remarkable clinical effects on psoriasis both in Caucasian and Asian ethnicities (8, 22-31). In contrast, the decisive pathogenic roles of IL-12, IFN-γ and IL-22 in psoriasis remain elusive, as clinical trials of the anti-IL-12 p35-p40 antibody (SMART), anti-IFN-γ antibody (HuZAF) and anti-IL-22 antibody (fezakinumab) have been discontinued (8).

Table 1. Comorbidity of Cardiovascular Diseases in Psoriasis.

References	Subjects	Brief description
Ref.41	Meta-analysis of 14 cohorts	Risk ratio relative to general population Cardiovascular disease mortality; 1.37 (95% CI 1.17-1.60) Myocardial infarction; 3.04 (95% CI 0.65-14.35) Stroke; 1.59 (95% CI 1.34-1.89)
Ref.42	German cross-sectional study (n=4,185) German Health Insurance beneficiaries (n=1,811,098)	Adjusted odds ratio Myocardial infarction; 2.26 (95% CI 1.03-4.96)
Ref.43	Control patients (n=556,995) Mild psoriasis (n=127,139) Severe psoriasis (n=3,837)	Adjusted relative risk in a 30-year old patient Myocardial infarction in mild psoriasis; 1.29 (95% CI 1.14-1.46) Myocardial infarction in severe psoriasis; 3.10 (95% CI 1.98-4.86)
Ref.44	Control patients (n=14,330) Severe psoriasis (n=3,603)	Adjusted relative risk in a 40-year old patient Cardiovascular mortality in severe psoriasis; 2.69 (95% CI 1.45-4.99)
Ref.46	Prospective study for 5.2 years follow-up Control patients (n=208,187) Psoriasis (n=48,523)	Fully adjusted hazard ratio Cardiovascular events; 1.02 (95% CI 0.95-1.08)
Ref.47	Hospital and clinic patients (n=113,065)	Adjusted odds ratio Coronary heart disease; 1.27 (95% CI 1.01-1.58) Hypertension; 7.78 (95% CI 7.25-8.36)
Ref.61	Control patients (n=24,285) Psoriasis (n=12,502)	Adjusted odds ratio Hypertension; 1.37 (95% CI 1.29-1.46)

High Clinical Burden in Psoriasis

Both the physical and psychological quality of life are significantly impaired in all populations of psoriasis sufferers (32-35), and patients' adherence to medication regimens and satisfaction with their results are very poor (36). The disease burden of psoriasis is further increased by its association with psoriatic arthritis, which is characterized by seronegative spondyloarthropathies, enthesitis and elevated C-reactive protein levels (5, 37-39). Approximately 15-30% of Caucasians with psoriasis eventually develop psoriatic arthritis (37). Although the prevalence is lower in Asian populations (Chinese 5.3-7.3%, Japanese 10.5% and Korean 11.2%), psoriatic arthritis significantly hampers patients' daily lives (37, 40). Additionally, psoriasis has significant comorbidity with CVD and metabolic syndrome.

Comorbidity with Cardiovascular Diseases

A recent meta-analysis and systematic review of 14 cohorts identified a CVD risk in individuals with severe psoriasis (defined as requiring systemic therapy or hospital admission): the risk ratio relative to the general population was 1.37 [95% confidence interval (CI): 1.17-1.60] for CVD mortality, 3.04 (95% CI: 0.65-14.35) for myocardial infarction and 1.59 (95% CI: 1.34-1.89) for stroke (41) (Table 1). The relative risks of CVD were highest in younger, more severe psoriasis patients [3.10 (95% CI: 1.98-4.86) for myocardial infarction at 30 years of age], and the absolute risks were greatest in older individuals with severe psoriasis (23.2 excess myocardial infarctions per 10,000 person-years at 60 years of age) (41). A German cross-sectional study that included 4,185 patients with psoriasis and a prospective cohort of German Health Insurance beneficiaries (n=1,811,098) showed that psoriasis was significantly associated with myocardial infarction (odds ratio: 2.26; 95% CI: 1.03-4.96) (42). In a longitudinal study, psoriasis slightly increased the incident risk for myocardial infarction (relative risk: 1.14; 95% CI: 1.06-1.22), with the highest risk increments found in systemically treated psoriasis, which accounted for 17 excess cases of myocardial infarction per 10,000 person-years (42). A significantly higher risk of myocardial infarction has been observed in psoriasis patients in the United Kingdom (43). For example, for a 30-year-old patient with mild or severe psoriasis, the adjusted relative risk of having a myocardial infarction is 1.29 (95% CI: 1.14-1.46) or 3.10 (95% CI: 1.98-4.86), respectively, compared with the control population (43). Furthermore, patients with severe psoriasis have an increased risk of CVD mortality that is independent of traditional CVD risk factors (44, 45). In a prospective cohort study that included 48,523 patients with psoriasis and 208,187 controls in the United Kingdom, 1,257 patients with psoriasis (2.59%) had a major CVD, compared with 4,784 controls (2.30%), during a median follow-up of 5.2 years (46). A multivariable analysis showed that the patients with psoriasis had significantly higher incidence of CVD than did the controls, with a hazard ratio (HR) 1.37 (95% CI: 1.29-1.45) for hypertension, HR 2.74 (95% CI: 2.41-3.12) for transient ischemic attack, HR 1.54 (95% CI: 1.36-1.73) for atrial fibrillation, HR 1.23 (95% CI: 1.05-1.44) for valvular heart disease, HR 1.32 (95% CI: 1.17-1.49) for thromboembolism and HR 1.57 (95% CI: 1.39-1.78) for congestive heart failure. The age- and gender-adjusted HRs of a major CVD for psoriasis were 1.10 (95% CI: 1.04-1.17) and 1.40 (95% CI: 1.07-1.84) for severe psoriasis (46).

A hospital-based study conducted by Shiba et al. in Japan analyzed the prevalence of coronary heart disease (n=5,167, 4.5%), hypertension (n=16,476, 14.5%), dyslipidemia (n=9,236, 8.1%), diabetes mellitus (n=11,555, 10.2%) and pso-

Table 2. Comorbidity of Metabolic Syndrome in Psoriasis.

References	Subjects	Brief description
Ref.42	German cross-sectional study (n=4,185) German Health Insurance beneficiaries (n=1,811,098)	Adjusted odds ratio Diabetes mellitus; 2.36 (95% CI 1.26-4.41)
Ref.45	Control patients (n=14,330) Psoriasis (n=3,603)	Adjusted hazard ratio Mortality from diabetes mellitus; 2.86 (95% CI 1.08-7.59)
Ref.46	Prospective study for 5.2 years follow-up Control patients (n=208,187) Psoriasis (n=48,523)	Adjusted hazard ratio Diabetes mellitus; 1.18 (95% CI 1.06-1.31)
Ref.47	Hospital and clinic patients (n=113,065)	Adjusted odds ratio Diabetes mellitus; 2.86 (95% CI 2.67-3.06) Dyslipidemia; 2.35 (95% CI 2.19-2.52)
Ref.51	Control patients (n=14,065) Severe psoriasis (n=3,854)	Adjusted odds ratio in severe psoriasis Diabetes mellitus; 1.62 (95% CI 1.3-2.01) Obesity; 1.79 (95% CI 1.55-2.05)
Ref.52	Control patients (n=6,643) Psoriasis (n=340)	Adjusted odds ratio Diabetes mellitus; 1.5 (95% CI 1.2-2.0) Dyslipidemia; 1.2 (95% CI 1.0-1.6) Obesity; 1.3 (95% CI 1.0-1.7)
Ref.53	Control patients (n=74,987) Psoriasis (n=16,851)	Adjusted odds ratio Diabetes mellitus; 1.58 (95% CI 1.49-1.68)
Ref.56	Danish population based twin study (n=34,781 twins)	Odds ratio Diabetes mellitus; 1.53 (95% CI 1.03-2.27) Obesity; 1.81 (95% CI 1.28-2.55)
Ref.57	Control patients (n=16,028) Psoriasis (n=429)	Odds ratio Obesity; 2.25 (95% CI 1.57-3.22)
Ref.60	Control patients (n=22,996) Psoriasis (n=10,669)	Adjusted odds ratio Dyslipidemia; 1.19 (95% CI 1.12-1.26)

riasis (n=1,197, 1.1%) in 113,065 patients (47). Their multivariate analysis showed that psoriasis was an independent variable associated with coronary heart disease (adjusted odds ratio: 1.27; 95% CI: 1.01-1.58; p=0.0404), hypertension (7.78; 95% CI: 7.25-8.36; p<0.0001), dyslipidemia (2.35; 95% CI: 2.19-2.52; p<0.0001) and diabetes (2.86; 95% CI: 2.67-3.06; p<0.0001) (47).

Comorbidity with Metabolic Syndrome

The association of psoriasis with metabolic syndrome (obesity, glucose intolerance, hypertension and dyslipidemia) has also been well documented (48, 49). As Henseler and Christophers reported in an earlier study (50), obesity and type 2 diabetes mellitus are significantly associated with psoriasis in the United Kingdom (51), Israel (52, 53), Italy (54), Germany (55) and Denmark (56) (Table 2). These results have been consistent with those for psoriasis patients in Japan (57), Korea (58) and Thailand (59). Psoriasis is also comorbid with other components of metabolic syndrome, such as dyslipidemia (51, 52, 60) and hypertension (51, 52, 55, 61). Furthermore, a significant association of psoriasis with dyslipidemia (58) and hypertension (59) has been reported in Asian populations. Moreover, patients with severe psoriasis had a higher prevalence of diabetes (51) and obesity (51) than did those with mild psoriasis. In this context, it is intriguing that dipeptidyl peptidase-4 inhibitors, a new class of antidiabetic agents, have been shown to improve skin symptoms in some psoriasis patients (62). Because topical vitamin D3 application is effective in treating psoriasis (63), the vitamin D3 level and bone mineral density have been assessed (64, 65). In those studies, the serum level of vitamin 25(OH)D3 was inversely correlated with the severity of psoriasis (64). Patients with a low bone mineral density showed a statistically significant longer average duration of psoriasis than those with better bone density (65).

Pathophysiology of Comorbidity

As mentioned above, psoriasis is a chronic inflammatory skin disease driven by the TNF-α / IL-23 / IL-17 axis (1, 4, 10). This notion is well supported by the high clinical efficacy of biologics against the TNF-α/IL-23/IL-17 pathway (5, 8, 15, 66). The release of excessive amounts of proinflammatory cytokines such as TNF-α and IL-1 may cause chronic low-grade systemic inflammation (67, 68) (Figure). The chronic state of inflammation appears to be a central mechanism underlying the pathophysiology of insulin resistance, visceral adiposity, hypertension and dyslipidemia. All of these conditions increase the risk for the development of type 2 diabetes and cardiovascular disease (67-69) (Figure). Consistent with this hypothesis, subclinical systemic and vascular inflammation have been detected by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with psoriasis (70). In a six-month prospective study, carotid arterial stiffness in patients with psoriasis was significantly improved by anti-

TNF-α therapy (71). In addition, other markers for systemic inflammation such as asymmetric dimethylarginine, red blood cell distribution width, the neutrophil-to-lymphocyte ratio, and the platelet-to-lymphocyte ratio, have proven to be upregulated in psoriatic patients (72-74).

In parallel with the above notions, the blockade of TNF-α by etanercept (anti-TNF-α treatment) improves the glucose tolerance in obese diabetic Zucker rats (75). Anti-TNF-α treatment with etanercept also suppresses cerebral damage caused by middle cerebral artery occlusion/reperfusion in both normal and diabetic rats (76). Furthermore, the inhibition of TNF-α production by a thalidomide analog decreases triglyceride levels and increases high-density lipoprotein levels in rats fed hypercholesterolemic diets (77).

Conclusion

Although the pathomechanisms of psoriasis are not fully understood, increasing research attention is being paid to the cutaneous-to-systemic expansion of the inflammatory process, which is now identified as the "psoriatic march" or "inflammatory skin march" (67, 68). This systemic inflammatory expansion is also seen in patients with severe eczema who have an increased risk for CVD (78). Another important fact related to "inflammatory skin march" is the significant association of psoriasis with other immune-mediated or autoimmune diseases such as inflammatory bowel disease (79, 80), multiple sclerosis (81) and autoimmune hepatitis (82). In addition, frequent comorbidity is noted in psoriasis and autoimmune bullous diseases (83-88). Further immunological studies into the genuine master switch underlying the comorbidity are warranted.

Finally, a disfigured appearance because of psoriasis may affect the psychological stability of patients (89). The cosmetic disfigurement associated with psoriasis increases the risk of depression, anxiety, feeling stigmatized and self-harm ideation, which profoundly impairs their satisfaction and adherence to medical care (36, 89, 90). In addition, internal physicians may hesitate to perform electrocardiogram, echocardiogram and even blood examinations, especially in severe cases with extensive skin eruption. These undesirable factors may delay the correct diagnosis and treatment of comorbid CVD and metabolic syndromes. As anti-TNF-α treatment is feasible for managing both skin lesions and comorbidities in psoriasis (12, 66), the early diagnosis and appropriate intervention by internal physicians in cooperation with dermatologists is required in order to increase the physical and mental quality of life in psoriatic patients.

The authors state that they have no Conflict of Interest (COI).

References

1. Libby P, Nahrendorf M, Swirski FK. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded "cardiovascular continuum". J Am Coll Cardiol **67**: 1091-1103, 2016.
2. de Souza Bastos A, Graves DT, de Melo Loureiro AP, et al. Diabetes and increased lipid peroxidation are associated with systemic inflammation even in well-controlled patients. J Diabetes Complications **30**: 1593-1599, 2016.
3. Herder C, Færch K, Carstensen-Kirberg M, et al. Biomarkers of subclinical inflammation and increases in glycaemia, insulin resistance and beta-cell function in non-diabetic individuals: the Whitehall II study. Eur J Endocrinol **175**: 367-377, 2016.
4. Joshi AA, Lerman JB, Aberra TM, et al. GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis. Circ Res pii: CIRCRESAHA.116.309637, 2016.
5. Boehncke WH, Schön MP. Psoriasis. Lancet **386**: 983-994, 2015.
6. Yin X, Low HQ, Wang L, et al. Genome-wide meta-analysis identifies multiple novel associations and ethnic heterogeneity of psoriasis susceptibility. Nat Commun **6**: 6916, 2015.
7. Kim J, Oh CH, Jeon J, et al. Molecular phenotyping small (Asian) versus large (Western) plaque psoriasis shows common activation of IL-17 pathway genes but different regulatory gene sets. J Invest Dermatol **136**: 161-172, 2016.
8. Furue M, Kadono T. Psoriasis: behind the scenes. J Dermatol **43**: 4-8, 2016.
9. Baurecht H, Hotze M, Brand S, et al. Genome-wide comparative analysis of atopic dermatitis and psoriasis gives insight into opposing genetic mechanisms. Am J Hum Genet **96**: 104-120, 2015.
10. Mabuchi T, Ota T, Manabe Y, et al. *HLA-C*12:02* is a susceptibility factor in late-onset type of psoriasis in Japanese. J Dermatol **41**: 697-704, 2014.
11. Feng C, Wang T, Li SJ, Fan YM, Shi G, Zhu KJ. *CARD14* gene polymorphism c.C2458T (p.Arg820Trp) is associated with clinical features of psoriasis vulgaris in a Chinese cohort. J Dermatol **43**: 294-297, 2016.
12. Piaserico S, Osto E, Famoso G, et al. Treatment with tumor necrosis factor inhibitors restores coronary microvascular function in young patients with severe psoriasis. Atherosclerosis **251**: 25-30, 2016.
13. Teng MW, Bowman EP, McElwee JJ, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med **21**: 719-729, 2015.
14. Lande R, Gregorio J, Facchinetti V, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature **449**: 564-569, 2007.
15. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol **32**: 227-255, 2014.
16. McGeachy MJ, McSorley SJ. Microbial-induced Th17: superhero or supervillain? J Immunol **189**: 3285-3291, 2012.
17. Ramírez-Valle F, Gray EE, Cyster JG. Inflammation induces dermal $V\gamma4^+$ $\gamma\delta$T17 memory-like cells that travel to distant skin and accelerate secondary IL-17-driven responses. Proc Natl Acad Sci USA **112**: 8046-8051, 2015.
18. Teunissen MB, Yeremenko NG, Baeten DL, et al. The IL-17A-producing $CD8^+$ T-cell population in psoriatic lesional skin comprises mucosa-associated invariant T cells and conventional T cells. J Invest Dermatol **134**: 2898-2907, 2014.
19. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity **34**: 149-162, 2011.
20. Ha HL, Wang H, Pisitkun P, et al. IL-17 drives psoriatic inflammation via distinct, target cell-specific mechanisms. Proc Natl Acad Sci USA **111**: E3422-E3431, 2014.
21. Reich K, Papp KA, Matheson RT, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol **24**: 529-535, 2015.
22. Torii H, Terui T, Matsukawa M, et al. Safety profiles and efficacy of infliximab therapy in Japanese patients with plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic

erythroderma: results from the prospective post-marketing surveillance. J Dermatol **43**: 767-778, 2016.
23. Asahina A, Torii H, Ohtsuki M, et al. Safety and efficacy of adalimumab treatment in Japanese patients with psoriasis: results of SALSA study. J Dermatol **43**: 1257-1266, 2016.
24. Asahina A, Ohtsuki M, Etoh T, et al. Adalimumab treatment optimization for psoriasis: results of a long-term phase 2/3 Japanese study. J Dermatol **42**: 1042-1052, 2015.
25. Kawakami H, Matsumoto Y, Abe N, et al. Perioperative management of tumor necrosis factor-alpha blocker-treated psoriatic patients: case reports and review. J Dermatol **43**: 190-193, 2016.
26. Kawakami H, Maeda T, Abe N, et al. Efficacy of adalimumab and methotrexate combination therapy on generalized pustular psoriasis patients unresponsive to infliximab monotherapy due to anti-infliximab antibody development. J Dermatol **42**: 94-95, 2015.
27. Takahashi H, Iinuma S, Tsuji H, Honma M, Iizuka H. Biologics are more potent than other treatment modalities for improvement of quality of life in psoriasis patients. J Dermatol **41**: 686-689, 2014.
28. Kusakari Y, Yamasaki K, Takahashi T, et al. Successful adalimumab treatment of a psoriasis vulgaris patient with hemodialysis for renal failure: a case report and a review of the previous reports on biologic treatments for psoriasis patients with hemodialysis for renal failure. J Dermatol **42**: 727-730, 2015.
29. Umezawa Y, Hayashi M, Kikuchi S, et al. Ustekinumab treatment in patients with psoriasis undergoing hemodialysis. J Dermatol **42**: 731-734, 2015.
30. Nimmannitya K, Tateishi C, Mizukami Y, et al. Successful treatment with ustekinumab of psoriasis vulgaris in a patient undergoing hemodialysis. J Dermatol **43**: 92-94, 2016.
31. Ohtsuki M, Morita A, Abe M, et al. Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study. J Dermatol **41**: 1039-1046, 2014.
32. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol **41**: 401-407, 1999.
33. Do YK, Lakhani N, Malhotra R, Halstater B, Theng C, Østbye T. Association between psoriasis and leisure-time physical activity: findings from the National Health and Nutrition Examination Survey. J Dermatol **42**: 148-153, 2015.
34. Ng CY, Yang YW, Liu SH, et al. SF-36 healty survey on psoriasis quality-of-life: a study of 414 Taiwanese patients. J Dermatol **42**: 159-165, 2015.
35. Atakan N, Yazici AC, Özarmağan G, et al. TUR-PSO: a cross-sectional, study investigating quality of life and treatment status of psoriasis patients in Turkey. J Dermatol **43**: 298-304, 2016.
36. Saeki H, Imafuku S, Abe M, et al. Poor adherence to medication as assessed by the Morisky Medication Adherence Scale-8 and low satisfaction with treatment in 237 psoriasis patients. J Dermatol **42**: 367-372, 2015.
37. Stuart PE, Nair RP, Tsoi LC, et al. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. Am J Hum Genet **97**: 816-836, 2015.
38. Asahina A, Umezawa Y, Yanaba K, Nakagawa H. Serum C-reactive protein levels in Japanese patients with psoriasis and psoriatic arthritis: long-term differential effects of biologics. J Dermatol **43**: 779-784, 2016.
39. Takata T, Takahashi A, Taniguchi Y, Terada Y, Sano S. Detection of asymptomatic enthesitis in psoriasis patients: an onset of psoriatic arthritis? J Dermatol **43**: 650-654, 2016.
40. Yamamoto T, Ohtsuki M, Sano S, et al. Epidemiological analysis of psoriatic arthritis patients in Japan. J Dermatol **43**: 1193-1196, 2016.
41. Samarasekera EJ, Neilson JM, Warren RB, Parnham J, Smith CH. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. J Invest Dermatol **133**: 2340-2346, 2013.
42. Koch M, Baurecht H, Ried JS, et al. Psoriasis and cardiometabolic traits: modest association but distinct genetic architectures. J Invest Dermatol **135**: 1283-1293, 2015.
43. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA **296**: 1735-1741, 2006.
44. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J **31**: 1000-1006, 2010.
45. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol **163**: 586-592, 2010.
46. Parisi R, Rutter MK, Lunt M, et al. Psoriasis and the risk of major cardiovascular events: cohort study using the clinical practice research datalink. J Invest Dermatol **135**: 2189-2197, 2015.
47. Shiba M, Kato T, Funasako M, et al. Association between psoriasis vulgaris and coronary heart disease in a hospital-based population in Japan. PLoS One **11**: e0149316, 2016.
48. Takahashi H, Iizuka H. Psoriasis and metabolic syndrome. J Dermatol **39**: 212-218, 2012.
49. Puig L, Kirby B, Mallbris L, Strohal R. Psoriasis beyond the skin: a review of the literature on cardiometabolic and psychological comorbidities of psoriasis. Eur J Dermatol **24**: 305-311, 2014.
50. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol **32**: 982-986, 1995.
51. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol **55**: 829-835, 2006.
52. Cohen AD, Gilutz H, Henkin Y, et al. Psoriasis and the metabolic syndrome. Acta Derm Venereol **87**: 506-509, 2007.
53. Cohen AD, Dreiher J, Shapiro Y, et al. Psoriasis and diabetes: a population-based cross-sectional study. J Eur Acad Dermatol Venereol **22**: 585-589, 2008.
54. Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol **157**: 68-73, 2007.
55. Schwandt A, Bergis D, Dapp A, et al. Psoriasis and diabetes: a multicenter study in 222078 type 2 diabetes patients reveals high levels of depression. J Diabetes Res **2015**: 792968, 2015.
56. Lønnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, Thomsen SF. Association of psoriasis with the risk for type 2 diabetes mellitus and obesity. JAMA Dermatol **152**: 761-767, 2016.
57. Naito R, Imafuku S. Distinguishing features of body mass index and psoriasis in men and women in Japan: a hospital-based case-control study. J Dermatol **43**: 1406-1411, 2016.
58. Choi WJ, Park EJ, Kwon IH, Kim KH, Kim KJ. Association between psoriasis and cardiovascular risk factors in Korean patients. Ann Dermatol **22**: 300-306, 2010.
59. Kokpol C, Aekplakorn W, Rajatanavin N. Prevalence and characteristics of metabolic syndrome in South-East Asian psoriatic patients: a case-control study. J Dermatol **41**: 898-902, 2014.
60. Dreiher J, Weitzman D, Davidovici B, Shapiro J, Cohen AD. Psoriasis and dyslipidaemia: a population-based study. Acta Derm Venereol **88**: 561-565, 2008.
61. Cohen AD, Weitzman D, Dreiher J. Psoriasis and hypertension: a case-control study. Acta Derm Venereol **90**: 23-26, 2010.
62. Nagai H, Fujiwara S, Takahashi Y, Nishigori C. Ameliorating effect of the novel dipeptidyl peptidase-4 inhibitor teneligliptin on psoriasis: a report of two cases. J Dermatol **42**: 1094-1097, 2015.
63. Mattozzi C, Paolino G, Richetta AG, Calvieri S. Psoriasis, vitamin D and the importance of the cutaneous barrier's integrity: an up-

date. J Dermatol **43**: 507-514, 2016.

64. Kincse G, Bhattoa PH, Herédi E, et al. Vitamin D_3 levels and bone mineral density in patients with psoriasis and/or psoriatic arthritis. J Dermatol **42**: 679-684, 2015.

65. D'Epiro S, Marocco C, Salvi M, et al. Psoriasis and bone mineral density: implications for long-term patients. J Dermatol **41**: 783-787, 2014.

66. Imafuku S, Honma M, Okubo Y, et al. Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: a 52-week analysis from phase III open-label multicenter Japanese study. J Dermatol **43**: 1011-1017, 2016.

67. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol **20**: 303-307, 2011.

68. Yamanaka K, Mizutani H. "Inflammatory skin march": IL-1-mediated skin inflammation, atopic dermatitis, and psoriasis to cardiovascular events. J Allergy Clin Immunol **136**: 823-824, 2015.

69. Welty FK, Alfaddagh A, Elajami TK. Targeting inflammation in metabolic syndrome. Transl Res **167**: 257-280, 2016.

70. Youn SW, Kang SY, Kim SA, Park GY, Lee WW. Subclinical systemic and vascular inflammation detected by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with mild psoriasis. J Dermatol **42**: 559-566, 2015.

71. Pina T, Corrales A, Lopez-Mejias R, et al. Anti-tumor necrosis factor-alpha therapy improves endothelial function and arterial stiffness in patients with moderate to severe psoriasis: a 6-month prospective study. J Dermatol **43**: 1267-1272, 2016.

72. Pina T, Genre F, Lopez-Mejias R, et al. Asymmetric dimethylarginine but not osteoprotegerin correlates with disease severity in patients with moderate-to-severe psoriasis undergoing anti-tumor necrosis factor-α therapy. J Dermatol **43**: 389-394, 2016.

73. Kim DS, Shin D, Jee H, et al. Red blood cell distribution width is increased in patients with psoriasis vulgaris: a retrospective study on 261 patients. J Dermatol **42**: 567-571, 2015.

74. Kim DS, Shin D, Lee MS, et al. Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis. J Dermatol **43**: 305-310, 2016.

75. Grauballe MB, Østergaard JA, Schou S, Flyvbjerg A, Holmstrup P. Effects of TNF-α blocking on experimental periodontitis and type 2 diabetes in obese diabetic Zucker rats. J Clin Periodontol **42**: 807-816, 2015.

76. Iwata N, Takayama H, Xuan M, et al. Effects of etanercept against transient cerebral ischemia in diabetic rats. Biomed Res Int **2015**: 189292, 2015.

77. Fumian MM, da Motta NA, Maia R, et al. LASSBio-1425, an analog of thalidomide, decreases triglyceride and increases HDL cholesterol levels by inhibition of TNF-α production. Int J Cardiol **202**: 497-499, 2016.

78. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol **135**: 721-728, 2015.

79. Egeberg A, Mallbris L, Warren RB, et al. Association between psoriasis and inflammatory bowel disease: a Danish nationwide cohort study. Br J Dermatol **175**: 487-492, 2016.

80. Nakamura K, Asano Y, Shibata S, et al. Case of psoriasis vulgaris developing ulcerative colitis during adalimumab treatment. J Dermatol **42**: 1029-1030, 2015.

81. Egeberg A, Mallbris L, Gislason GH, Skov L, Hansen PR. Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. J Invest Dermatol **136**: 93-98, 2016.

82. Jensen P, Egeberg A, Gislason G, Hansen PR, Thyssen JP, Skov L. Increased risk of autoimmune hepatitis in patients with psoriasis: a Danish nationwide cohort study. J Invest Dermatol **136**: 1515-1517, 2016.

83. Takahashi H, Sato K, Takagi A, et al. Subepidermal autoimmune blistering lesion in a case of psoriasis successfully treated with cyclosporin. J Dermatol **42**: 1125-1126, 2015.

84. Maki N, Demitsu T, Umemoto N, et al. Possible paraneoplastic syndrome case of bullous pemphigoid with immunoglobulin G anti-BP180 C-terminal domain antibodies associated with psoriasis and primary macroglobulinemia. J Dermatol **43**: 571-574, 2016.

85. Okahashi K, Oiso N, Ishii N, et al. Bullous pemphigoid associated with psoriasis: a possible example of an inverse intramolecular epitope-spreading phenomenon. J Dermatol **42**: 758-759, 2015.

86. Ishida S, Takahashi K, Kanaoka M, et al. Case of subepidermal autoimmune bullous disease with psoriasis vulgaris reacting to both BP180 C-terminal domain and laminin gamma-1. J Dermatol **42**: 391-393, 2015.

87. Imanishi A, Tateishi C, Imanishi H, et al. Pemphigoid with antibodies to laminin γ1, BP180 and BP230, associated with psoriasis vulgaris: successful disease control with cyclosporin. J Dermatol **42**: 394-397, 2015.

88. Ansai S, Hashizume S, Kawana S, Tateishi C, Koga H, Hashimoto T. Case of anti-laminin gamma-1 pemphigoid with antibody against C-terminal domain of BP180 in a patient with psoriasis vulgaris. J Dermatol **41**: 1031-1033, 2014.

89. Tomas-Aragones L, Marron SE. Body image and body dysmorphic concerns. Acta Derm Venereol **96**: 47-50, 2016.

90. Offidani E, Del Basso D, Prignago F, Tomba E. Discriminating the presence of psychological distress in patients suffering from psoriasis: an application of the clinimetric approach in dermatology. Acta Derm Venereol **96**: 69-73, 2016.