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EDITORIAL

Metabolic co-morbidities and psoriasis: The chicken or the egg?

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Abstract

Accumulating evidence supports that psoriasis may be a potential multisystem inflammatory disease associated with a range of co-morbidities showing an overlapping pathology and an important health impact such as metabolic diseases. Psoriasis is associated with an increased risk of obesity, metabolic syndrome (Mets) and diabetes mellitus type 2, following a "dose-response" relationship from mild to severe psoriasis. Conversely, recent evidence from large prospective studies suggests that obesity constitutes a risk factor for psoriasis and psoriatic arthritis. Also, a dyslipidemic profile may precede psoriasis onset. Both obesity, Mets and psoriasis, characterized as chronic inflammatory states, stem from a shared underlying pathophysiology exhibiting common genetic predisposition and risk factors such as high caloric intake, physical inactivity and psychological stress. Excess weight may potentiate the inflammation of psoriasis through the deregulation of adipocytokines while, at the same time, it may help the development of Mets. Interestingly, recent translational data has shown that psoriasis, through increased T-helper inflammatory cytokines in skin and sera, may exert a plethora of effects on insulin regulation and lipid metabolism. Larger population-based prospective cohort and longitudinal studies are needed to unravel the association between psoriasis and metabolic co-morbidities. The recognition of the intricate complex interplay between psoriasis and metabolic co-morbidities may help dermatologists to be aware of associated metabolic co-morbidities in order to screen for metabolic diseases and manage holistically and effectively the psoriatic patient.

Key words: Psoriasis; Obesity; Metabolic syndrome; Metabolic co-morbidities; Diabetes mellitus; Insulin resistance

Core tip: Psoriasis is associated with an increased risk of obesity, metabolic syndrome (Mets) and diabetes mellitus type 2, following a "dose-response" relationship from mild to severe psoriasis. Conversely, recent evidence from large prospective studies suggests that obesity constitutes a risk factor for psoriasis and psoriatic arthritis. Both obesity, Mets and psoriasis, characterized as chronic inflammatory states, stem from a shared underlying pathophysiology exhibiting common genetic predisposition and risk factors such as high caloric intake, physical inactivity and psychological stress. Larger population-based prospective cohort and longitudinal studies are needed to unravel the association between psoriasis and metabolic co-morbidities.

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INTRODUCTION

Psoriasis is a chronic, systemic, T-cell immune-mediated inflammatory skin disorder characterized by dermal and

joint manifestations[1,2]. The prevalence of psoriasis varies approximately from 0.1% to 3.0% worldwide, with a mean prevalence rate of 1.90% in Western countries and a lower prevalence elsewhere[3].

Its etiology is unknown; however, the interplay between genetic susceptibility and exogenous environmental factors plays an important role[2]. Several human leukocyte antigen (HLA) alleles including HLA-Cw*0602 and non-HLA related genes such as interleukin (*IL*)-*12B* and *IL-23R* genes are associated with psoriasis risk[1,4].

PSORIASIS AS A CHRONIC INFLAMMATORY DISEASE

There is accumulating evidence that the characteristic T-helper (Th)-1 chronic inflammation seen in the psoriatic plaque may be connected with the systemic chronic inflammatory process seen in atherosclerosis and insulin resistance through various inflammatory mediators and cells[5]. The contribution of T cells to psoriasis pathophysiology shows the extent of its systemic involvement. Indeed, Th-1, Th-17 and Th-22 cell populations are expanded and enhanced to secrete inflammatory cytokines, comprising tumor necrosis factor-α (TNF-α), IL-17 and IL-22[1,2]. The psoriatic inflammatory pathology may play a role in immune and metabolic changes that contribute to the perpetuation of psoriasis and the development of co-morbidities[3,6]. In contrast to rheumatoid arthritis, psoriasis is not a systematic disease *per se* with multi-organ involvement (except joints); however, accumulating medical evidence supports the assertion that psoriasis may be a potential multisystem inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and an important health impact such as metabolic diseases, cardiovascular disease (CVD), autoimmune disease, psychiatric disorders, malignancy, chronic obstructive pulmonary disease and sleep apnea[2,7,8].

PSORIASIS AND THE RISK OF METABOLIC CO-MORBIDITIES

Metabolic diseases such as obesity, insulin resistance, metabolic syndrome (Mets), diabetes type 2 (t2DM) and dyslipidemia occur at a higher frequency in psoriatics than in general population[3,9-12]. Indeed, substantial evidence shows that psoriasis is associated with an increased risk of obesity[3,9]. Obesity is more common in psoriatic arthritis (PsA) than in rheumatoid arthritis[11]. Central or abdominal obesity represents an important component of Mets along with impaired glucose tolerance, elevated blood pressure and dyslipidemia. A recent meta-analysis has provided further evidence that psoriatic patients present a higher prevalence of Mets than the general population[13]. In particular, the prevalence of Mets in psoriatic patients is higher than that of the general population, being 40% in the United States and 27.4% in Japan[9]. Additionally, patients with PsA present significantly higher prevalence of Mets compared to the general population[3]. Whether the connection between Mets, obesity and psoriasis is valid for the full spectrum of psoriasis patients or only for those with more severe psoriasis remains controversial. Nonetheless, psoriasis was independently associated with Mets and followed a "dose-response" relationship from mild to severe psoriasis[10,11]. Also, obesity as expressed by the body mass index (BMI) was positively associated with psoriasis area and severity index (PASI) score[10-13]. The parameters defining Mets go hand in hand with an elevated risk for t2DM and CVD while emerging data indicate that psoriasis could be an independent risk factor for CVD[6]. Psoriasis patients demonstrate more frequently insulin resistance compared to healthy controls when challenged with oral glucose tolerance test and present an increased risk of t2DM, particularly female patients[6,12]. The adjusted risk ratios for t2DM risk following psoriasis vary between 1.08 and 3.61[12], being somewhat stronger in Asian than in European and American studies[12]. The risk of t2DM increases in patients with psoriasis and PsA with BMI, psoriasis severity and duration[11]. Finally, psoriasis patients are at increased risk for non-alcoholic fatty liver disease and liver fibrosis compared to healthy controls[10].

Both psoriasis and metabolic co-morbidities share common genetic predisposition. For example, the psoriasis genetic risk loci *PSORS* 2-4 and *CDKAL1* are associated with susceptibility of t2DM[12]. Furthermore, psoriasis and metabolic co-morbidities share common risk factors such as smoking, weight gain, physical inactivity and psychological stress[9]. Psoriatics are more likely to lead unhealthy lifestyles and to present psychological impairment suffering thus, from obesity, Mets, t2DM, anxiety and depression as a result. Moreover, severe psoriasis greatly affects patients and is associated with habits (*i.e.,* eating, smoking, alcohol) and states of mind (*i.e.,* depression) that may represent risk factors for metabolic co-morbidities[8]. Hence, all these genetic, lifestyle parameters and the underlying chronic systemic psoriatic inflammation may contribute in tandem to an increased risk for metabolic co-morbidities and CVD.

METABOLIC DISEASES AND THE RISK OF PSORIASIS

Although there is a strong association between psoriasis and metabolic diseases, the etiology of this link remains enigmatic. Whether excess weight is a predisposing factor or a manifestation of psoriasis is still controversial. Recent evidence from large prospective studies suggests that obesity constitutes a risk factor for psoriasis and PsA development[6,11,14]. Additional data have revealed that a dyslipidemic profile characterized by elevated triglycerides, total and low-density lipoprotein cholesterol as well as decreased high-density lipoprotein levels precedes psoriasis onset[9,15]. Whether obesity and its metabolic complications are the causes or the effects of psoriasis,

the obese state may exacerbate the severity of psoriasis as confirmed in a number of cross-sectional studies whereas increased BMI correlates positively with PASI and psoriasis area[6].

Both obesity, Mets and psoriasis, characterized as chronic inflammatory states, stem from a shared underlying pathophysiology. Apart from its energy storage function, adipose tissue is a genuine endocrine organ secreting several bioactive adipocytokines regulating physiological and pathological processes, including appetite, insulin sensitivity and resistance, immunity, and inflammation[16-19]. Increased adiposity following weight gain is associated with elevated levels of adipocytokines, comprising TNF-α, IL-6, leptin, resistin and visfatin, and decreased levels of adiponectin, that may promote immune stimulation, leading to both Th1 and Th17 immune responses and impairing the function of T regulatory cells[16-18]. In parallel, the etiopathogenesis of Mets is attributed to hyperinsulinemia and insulin resistance mediated by adipocytokines, such as TNF-α, leptin, adiponectin and resistin[9,18-20]. It seems that obesity may potentiate the inflammation of psoriasis while, at the same time, it may help the development of Mets. Hence, adipocytokines may be a missing link in the association between metabolic co-morbidities and psoriasis, and could be used as potential biomarkers for assessing disease severity and risk of co-morbidities[20]. Conversely, it is now recognized from translational data that psoriasis, as a chronic inflammatory systemic disease through TNF-α and T-helper inflammatory cytokines that are increased in skin and sera, may exert a plethora of effects on insulin regulation and lipid metabolism which are important in the pathophysiology of metabolic co-morbidities[9-11].

UNRAVELING THE VICIOUS CYCLE OF PSORIASIS AND METABOLIC CO-MORBIDITIES

A vicious cycle is established whereby weight gain and Mets may play a pivotal role in psoriasis, and, as psoriasis progresses in severity and chronicity, obesity and metabolic co-morbidities may be more pronounced due to enhanced caloric intake, physical inactivity and unhealthy habits caused by psychological factors in psoriasis and PsA[21,22].

In order to unmask the association between psoriasis and metabolic co-morbidities, evidence is needed from adequately powered, large, long-term, population-based prospective cohort and longitudinal studies taking into account in multivariable statistical analyses important parameters such as anthropometric variables (*i.e.*, BMI, waist circumference), metabolic factors (*i.e.*, glucose, insulin, homeostasis model assessment scores), habits (*i.e.*, smoking, alcohol) and psoriasis systematic treatment.

The recognition of the intricate complex interplay between psoriasis and metabolic co-morbidities may help dermatologists to be aware of associated metabolic co-morbidities in order to screen for metabolic diseases and manage holistically and effectively the psoriatic patient. Lifestyle interventions, diet, physical activity and management of metabolic co-morbidities may be beneficial for psoriasis patients by improving both their physical and psychological well being and prolonging their lifespan. More studies are also needed to study the effect of psoriasis systemic therapies on metabolic co-morbidities and to unravel the mechanisms of the underlying association between psoriasis and metabolic co-morbidities.

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