

Relationship between bullous pemphigoid and metabolic syndrome: a 12-year case–control study conducted in China

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Abstract

Background: Hypertension, diabetes, dyslipidemia, and obesity are prevalent in patients with bullous pemphigoid (BP) and are all components of metabolic syndrome (MS). However, the prevalence of MS in patients with BP is unknown. We aimed to evaluate the relationship between MS and BP and to define the clinical and laboratory characteristics of patients with both conditions.

Methods: This retrospective case–control study was conducted for 12 years at Peking Union Medical College (162 with BP and 162 age and sex-matched controls). The components of MS were analyzed and logistic regression was used to identify independent risk factors for BP. In addition, the clinical and laboratory characteristics of patients with BP ± MS were compared.

Results: The prevalence of MS in patients with BP was 35.2% and that in controls was 14.8% ($p < 0.001$). After adjustment for sex and age, multivariate analysis demonstrated a positive correlation between BP and MS [odds ratio (OR) 2.490, 95% confidence interval (CI) 1.040–5.963], diabetes (OR 1.870, 95% CI 1.029–3.396), and overweight or obesity (OR 1.807, 95% CI 1.026–3.182). In the BP group, participants with MS were older ($p = 0.006$), were less likely to present erythema ($p = 0.028$), and had higher serum C3 ($p = 0.007$) and incidence of infection within 1 year of their diagnosis ($p = 0.035$) than participants without MS.

Conclusion: MS and its components hyperglycemia and overweight were found to be independently associated with BP. Therefore, clinicians should screen for MS in patients with BP, especially if they are older, present less erythema, or have a high serum C3.

Keywords: bullous pemphigoid, metabolic syndrome, hyperglycemia, overweight

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Introduction

Bullous pemphigoid (BP) is the most common autoimmune sub-epidermal blistering disorder. It is characterized by the presence of autoantibodies that target components of the basement membrane, and clinically by tense blisters that may develop on normal or erythematous skin. BP mainly affects individuals of 60–80 years old, and it has been reported that the annual incidence of BP is between 2.4 and 21.7 new cases per million in populations around the world.¹ Although this incidence is relatively low, it appears to be increasing,² with estimates of the increase over the past

two decades ranging from 1.9- to 4.3-fold.^{3–6} Therefore, it is important to identify potentially modifiable risk factors for BP.

Metabolic syndrome (MS) is a set of cardiovascular risk factors that includes obesity, dyslipidemia, hypertension, and impaired glucose tolerance. Because the prevalence of MS varies according to sex, age, race, ethnicity, and region, there is no universal set of diagnostic criteria for MS. However, the widely accepted criterion used in China, developed by the Chinese Diabetes Society (CDS) in 2004, is the presence of at least

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three of the following: overweight or obesity [body mass index (BMI) ≥ 25.0 kg/m²], hypertension [systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or a history of hypertension], hyperglycemia [fasting blood glucose (FBG) ≥ 6.1 mmol/L or a history of diabetes], and dyslipidemia [triglycerides (TG) ≥ 1.7 mmol/L and/or high-density lipoprotein-cholesterol (HDL-C) < 0.9 mmol/L for men and < 1.0 mmol/L for women].⁷ As a consequence of the development of society and economy in China, the dietary composition and lifestyle of the population have changed significantly, which has led to an increase in the prevalence of MS and a substantial public health challenge.⁸

There is increasing evidence that BP is a systemic immune-mediated disease, rather than an isolated skin immunological disease. Previous studies have shown links between BP and systemic conditions, such as hypertension, obesity, dyslipidemia, and insulin resistance. In a Finnish cohort, the most common comorbidities in patients with BP were found to be hypertension (44%) and type 2 diabetes (34%).⁹ A large-scale US study of data collected between 2002 and 2012 showed that BP was clearly associated with diabetes and obesity.¹⁰ Finally, a cross-sectional study conducted in Morocco showed that the most common comorbidities of BP were hypertension (58%), type 2 diabetes (43%), and dyslipidemia (31%).¹¹ However, the relationship between BP and these conditions, which together comprise MS, has not been studied previously, and the relationship is likely to be substantially affected by medication. For example, gliptins and diuretics may be at least in part responsible for the onset of BP in patients with type 2 diabetes or hypertension,¹² and glucocorticoid therapy of BP may cause changes in blood glucose, blood pressure, circulating lipids, and body mass, and therefore affect the onset of MS.

In this study, we aimed to evaluate the relationship between BP and MS by excluding patients with possible drug-induced BP and comparing the characteristics of patients with untreated new-onset BP with healthy controls. In addition, we aimed to define the clinical and laboratory characteristics of patients with both BP and MS.

Patients and methods

Participants and matching

This retrospective case-control study was approved by the Ethics Committee of Peking Union Medical College Hospital (Number: S-K1853) and written informed consent was obtained from all the participants. We identified patients who had been newly diagnosed with BP at Peking Union Medical College Hospital between January 2009 and May 2021. The diagnosis of BP was based on the S2k guidelines for the diagnosis of BP.¹³ The exclusion criteria were (1) a lack of sufficient documentation to support a diagnosis of BP or MS, (2) previous systemic treatment with a corticosteroid or immunosuppressant, and (3) probable or possible drug-induced BP. The assessment of causality was performed using the World Health Organization-Uppsala Monitoring Center system for the standardized assessment of disease causality in patients. The control group consisted of patients undergoing assessment for osteoarticular injury, in whom diagnosis of BP, hypereosinophilic dermatitis, or eczema had been excluded. The controls were matched 1:1 to the cases according to their age, sex, and index year.

Data collection

A diagnosis of MS was made on the basis of the CDS criteria. The participants' height and body mass were recorded for the calculation of BMI. Blood pressure was measured using an electronic sphygmomanometer after 10 minutes of rest in a sitting position. The blood pressure of inpatients was measured twice a day during hospitalization, and the outpatients were advised to monitor their blood pressure before and after treatment based on the standards for accurate blood pressure measurement and record it in a designated form. Venous blood samples were drawn for biochemical analysis following at least 12 h of fasting. FBG, serum TG, serum HDL-C, serum anti-BP180-NC16A IgG, serum total IgE, eosinophil count, serum C3, serum C4, indirect immunofluorescence (IIF), and direct immunofluorescence (DIF) data were measured in the clinical laboratory of our hospital. In addition, the age at the diagnosis of BP, sex, hospitalization data, history of smoking and drinking, type and distribution of skin lesions, bullous pemphigoid disease

area index (BPDAI) score, therapy, and details of any infections were obtained from the participants' electronic medical records.

Statistical analysis

Since the prevalence of MS in patients with BP has not been reported in the previous literature, it is difficult to estimate sample size before the study. Therefore, we included as many cases as possible at Peking Union Medical College Hospital between January 2009 and May 2021, and selected matched controls (1:1). The power analysis was conducted using NCSS-PASS software and determined that our findings with a sample size of 162 BP patients and 162 controls were powered to detect a difference in MS rates for cases and controls (power of 99.9%, $\alpha = 0.05$).

Data were analyzed using SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, N.Y., USA). The normality of continuous data sets was assessed using the Shapiro–Wilk test. Continuous data sets with normal distributions are presented as mean \pm standard deviation and were analyzed using Student's *t*-test. Non-normally distributed data sets are presented as median and interquartile range (IQR) and were analyzed using the Mann–Whitney *U*-test. Categorical data sets are expressed as an absolute number and percentage and were analyzed using the chi-square test. Multivariate analysis was performed using a multiple binary logistic regression model, incorporating the parameters that were found to be significant using univariate analysis. $P < 0.05$ (two-sided) was considered to represent statistical significance.

Results

Baseline characteristics

Between January 2009 and May 2021, 179 patients with newly diagnosed BP were initially included, but 17 were subsequently excluded because of probable or possible drug-induced BP according to the World Health Organization–Uppsala Monitoring Center system. Thus, a total of 162 patients with BP were enrolled, of whom 87 (53.7%) were men and 75 (46.3%) were women. Their median age at diagnosis was 68.0 (interquartile range, 57.0–79.0) years. The control group consisted of 162 patients with osteoarticular injury,

in which diagnosis of BP, hypereosinophilic dermatitis, or eczema had been excluded. The control participants were matched 1:1 on the basis of age, sex, and index year with those with BP. More details are provided in Table 1.

Univariate and multivariate logistic regression analysis

Univariate analysis demonstrated that individuals with BP had significantly higher median FBG [5.6 (5.0–6.6) mmol/L vs 4.9 (4.6–5.4) mmol/L, $P < 0.001$] and HDL-C [1.2 (1.0–1.5) mmol/L vs 1.1 (0.9–1.3) mmol/L, $p = 0.042$]; and higher prevalences of MS [57 (35.2%) vs 24 (14.8%), $P < 0.001$], hyperglycemia [62 (38.3%) vs 34 (21.0%), $P = 0.001$], and overweight or obesity [72 (44.4%) vs 42 (25.9%), $p < 0.001$], than the controls. There were no differences in the other parameters (smoking status, alcohol consumption, SBP, DBP, TG, and BMI) between the two groups (Table 1).

Multivariate logistic regression analysis was used to further evaluate the relationships of BP with MS and its components and showed positive associations of BP with diabetes [odds ratio (OR) 1.870, 95% confidence interval (CI) 1.029–3.396], overweight or obesity (OR 1.807, 95% CI 1.026–3.182), and MS (OR 2.490, 95% CI 1.040–5.963) after adjustment for sex and age (Table 2).

Characterization of patients with BP and MS

A comparison of participants with BP \pm MS showed that those with MS were older when BP was diagnosed [72.0 (66.0–80.0) years vs 65.0 (54.5–76.5) years, $P = 0.006$], were less likely to present erythema [39 (69.6%) vs 87 (84.5%), $P = 0.028$], had higher serum C3 (1.2 ± 0.1 g/L vs 1.0 ± 0.2 g/L, $P = 0.007$), and had a higher incidence of infection within the first year of the diagnosis of BP [14 (66.7%) vs 11 (36.6%), $P = 0.035$] than those without MS. There were no significant differences between the groups with regard to their other clinical and laboratory characteristics, including sex ratio, requirement for hospitalization, mucosal involvement, BPDAI score, serum total IgE, anti-BP180 NC16A IgG autoantibody (determined using enzyme-linked immunosorbent assay), serum C4, eosinophil count, IIF, DIF, therapy, and the site of infection (Table 3).

Table 1. Demographic and anthropometric characteristics of participants with BP and controls.

Variable	Bullous pemphigoid (N = 162)	Controls (N = 162)	P value
Age, years	68.0 (57.0–79.0)	68.0 (55.0–79.0)	0.921
<40, n (%)	5 (3.1%)	5 (3.1%)	
40–59, n (%)	47 (29.0%)	47 (29.0%)	
60–79, n (%)	74 (45.7%)	74 (45.7%)	
≥80, n (%)	36 (22.2%)	36 (22.2%)	
Sex			1.000
Male, n (%)	87 (53.7%)	87 (53.7%)	
Female, n (%)	75 (46.3%)	75 (46.3%)	
Current/ex-smoker, n (%)	32 (33.7%)	44 (27.1%)	0.269
Alcohol consumption, regular/heavy, n (%)	21 (22.1%)	28 (17.3%)	0.342
SBP, mmHg	129.0 ± 18.5	130.6 ± 16.4	0.472
DBP, mmHg	75.1 ± 11.5	75.1 ± 9.9	0.958
FBG, mmol/L	5.6 (5.0–6.6)	4.9 (4.6–5.5)	<0.001*
TG, mmol/L	1.2 (0.9–1.7)	1.1 (0.8–1.6)	0.579
HDL-C, mmol/L	1.2 (1.0–1.5)	1.1 (0.9–1.3)	0.042*
BMI, kg/m ²	24.4 ± 4.0	23.7 ± 2.7	0.060
Metabolic syndrome, n (%)	57 (35.2%)	24 (14.8%)	<0.001*
Blood pressure ≥ 140/90 mmHg or hypertension history, n (%)	88 (54.3%)	74 (45.7%)	0.120
FBG ≥ 6.1 mmol/L or diabetes history, n (%)	62 (38.3%)	34 (21.0%)	0.001*
TG > 1.7 mmol/L or/and HDL-C < 1.0 mmol/L (male) or < 1.3 mmol/L (female), n (%)	74 (45.7%)	60 (37.0%)	0.114
Overweight or obesity, n (%)	72 (44.4%)	42 (25.9%)	<0.001*

BP, bullous pemphigoid; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TG, triglyceride.
**p* < 0.05 vs control group.

Discussion

MS is a cluster of risk factors for cardiovascular disease that includes obesity, dyslipidemia, hypertension, and impaired glucose tolerance. Relationship between MS and many chronic inflammatory skin disorders have been reported,

including psoriasis,^{14,15} atopic dermatitis,¹⁶ and hidradenitis suppurativa.^{17,18}

BP is considered to be an autoimmune subepidermal blistering disease involving inflammatory responses in the pathogenesis. Many previous

studies have shown associations between BP and cardiovascular risk factors, suggesting a possible link between BP and MS. During the past decade, a number of case-control studies^{9,10,19–22} have shown a strong association between BP and diabetes, whereas others have not.^{23–28} Similarly, hypertension has been shown to be significantly associated with BP in many case-control studies,^{19–24,29} but not under all circumstances.^{9,10,25–27} A few studies have shown a negative association between hyperlipidemia and BP,²⁴ but others have not shown any relationship.^{19,21} In addition, two large population-based studies conducted in the United States showed a significant association between obesity and BP.^{10,22} However, the use of medication before a diagnosis of BP and the treatment of BP with glucocorticoids or immunosuppressants may confound the relationship between components of MS and BP.

To the best of our knowledge, this is the first study to assess the prevalence of MS in patients with BP and to provide evidence for an association between MS and BP. We found a high prevalence (35.2%) of MS in a cohort of patients with new-onset BP, compared with a prevalence of 14.8% in the control group. Of the components of MS, hyperglycemia and overweight or obesity were respectively present in 38.3% and 44.4% of the participants with BP, which are significantly higher percentages than in the control group. The laboratory data regarding components of MS showed that the BP group had significantly higher FBG concentrations than the control group. Contrary to expectations, the serum HDL-C was lower in the control group than in the BP group, but this has been shown previously.²⁴ Multivariate logistic regression analysis confirmed that MS, overweight or obesity, and hyperglycemia are independent risk factors for BP.

The mechanisms underpinning the relationship between the two diseases remain to be investigated. Inflammation underpins the adipose tissue dysfunction that characterizes MS and is associated with higher concentrations of pro-inflammatory cytokines and other factors, and alterations in adipokine secretion,³⁰ which may cause skin inflammation. Kulkarni *et al.*³¹ showed that an animal model of MS and non-alcoholic fatty liver disease is characterized by the presence of skin inflammation, which is consistent with such an interaction between adipose tissue and skin. This

Table 2. Risks of bullous pemphigoid associated with individual components of the metabolic syndrome.

Variable	β	OR	95% CI	P value
Hypertension				
Unadjusted	-0.327	0.721	0.437–1.189	0.200
Adjusted	-0.285	0.752	0.449–1.126	0.279
Hyperglycemia				
Unadjusted	0.595	1.813	1.011–3.252	0.046*
Adjusted	0.626	1.870	1.029–3.396	0.040*
Dyslipidemia				
Unadjusted	-0.296	0.744	0.424–1.306	0.303
Adjusted	-0.292	0.747	0.425–1.312	0.310
Overweight or/and obesity				
Unadjusted	0.592	1.807	1.031–3.165	0.039*
Adjusted	0.592	1.807	1.026–3.182	0.041*
Metabolic syndrome				
Unadjusted	0.931	2.537	1.062–6.061	0.036*
Adjusted	0.912	2.490	1.040–5.963	0.029*

CI, confidence interval; OR, odds ratio.
* $P < 0.05$. Data were adjusted for sex and age.

finding suggests that a pro-inflammatory milieu may explain the association between BP and MS. Furthermore, MS is associated with an increase in thrombogenicity, and the activation of the coagulation system increases the permeability of blood vessels and infiltration with pro-inflammatory cells, which may contribute to the inflammation, tissue damage, and blister formation of patients with BP.^{32–34}

In addition, we have defined the clinical and laboratory features of patients with BP and MS. We found that patients with coexisting BP and MS were older than those with BP alone, which can be explained by the tendency for MS to develop in older people. Interestingly, our findings suggest that patients with BP and MS have higher serum C3 concentrations than in those without MS. High C3 concentration has also been shown to be an independent risk factor for MS and cardiovascular disease in patients with SLE.³⁵

Table 3. Comparison of the clinical and laboratory characteristics of patients with BP ± MS.

Variable	With MS (N = 57)	Without MS (N = 105)	P value
Age at diagnosis, mean ± SD, years	72.0 (66.0–80.0)	65.0 (54.5–76.5)	0.006*
Sex			
Male	32 (56.1%)	55 (52.4%)	0.647
Female	25 (43.9%)	50 (47.6%)	
Hospitalization			
Number of inpatients, n (%)	33 (57.9%)	51 (48.6%)	0.257
Duration, mean ± SD, day	21.0 (14.0–27.0)	17.0 (12.0–24.0)	0.482
Urticaria erythema	39 (69.6%)	87 (84.5%)	0.028*
Mucosal involvement	15 (26.8%)	24 (23.8%)	0.675
BPDAI score	112.3 ± 61.4	77.4 ± 22.2	0.194
BP180 NC16A ELISA			
Seropositivity, n (%)	40 (80.0%)	73 (84.9%)	0.464
ELISA value, U/L	50.0 (20.8–109.3)	75.0 (28.8–134.8)	0.231
IIF seropositivity	35 (79.5%)	59 (68.6%)	0.187
Linear deposits of immunoreactants by DIF			
IgG	18 (48.6%)	44 (58.7%)	0.316
IgM	1 (2.7%)	3 (4.0%)	0.728
C3	22 (59.5%)	49 (65.3%)	0.544
Eosinophil count, cells/L	0.2 (0.1–0.8) × 10 ⁹	0.4 (0.1–1.2) × 10 ⁹	0.225
IgE autoantibody, KU/L	638.0 (135.0–3736.0)	722.0 (149.0–2222.0)	0.793
Serum C3, g/L	1.2 ± 0.1	1.0 ± 0.2	0.007*
Serum C4, g/L	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.345
Treatment			
Oral prednisone, n (%)	43 (75.4%)	86 (81.9%)	0.329
Control dose of corticosteroid, mg/d	40 (30–60)	45 (30–60)	0.249
Adjuvant immunosuppressant, n (%)	29 (50.9%)	60 (57.7%)	0.406
Biological agent, n (%)	3 (5.5%)	3 (2.9%)	0.426
Only topical steroids, n (%)	7 (12.3%)	5 (4.8%)	0.081
Infection within 1 year	14 (66.7%)	11 (36.6%)	0.035*
Lung	6 (42.9%)	4 (36.4%)	0.742
Skin	5 (35.7%)	4 (36.4%)	0.973
Blood	2 (14.3%)	2 (18.2%)	0.792

BP, bullous pemphigoid; BPDAI, bullous pemphigoid disease area index; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; MS, metabolic syndrome; SD, standard deviation.

**p* < 0.05 vs control group.

Moreover, specific C3 polymorphisms have been shown to predict future cardiovascular events in the general population.³⁶ A possible explanation for the association between high serum C3 and MS in patients with BP might be greater production of C3 in the liver and adipose tissue in obesity.³⁶ We compared the medication used and the response to treatment of participants with BP \pm MS and found no significant differences in the use of glucocorticoids, immunosuppressants, or biological agents between the two groups. The dose of glucocorticoid used to control disease in the participants with both BP and MS was slightly, but not significantly, lower. The reason for this may be that clinicians tend to use lower doses of glucocorticoids in patients with MS, to avoid potential complications. In addition, the participants with both BP and MS were more likely to experience an infection within 1 year of their diagnosis of BP, and the principal sites of infection were the lungs, skin, and blood. Therefore, clinicians should consider this potential complication when designing treatment strategies.

Some limitations of this study should be acknowledged. First, the prevalence of MS varies according to the diagnostic criteria used. Some international organizations recommend the use of waist circumference as an index of central obesity,³⁷ rather than BMI, which was used in this study. We did not assess the prevalence of MS using alternative sets of diagnostic criteria, which limits the generalizability of the findings. Second, other factors that have been shown to be associated with MS were not assessed, including geographical location, exercise status, educational level, and economic circumstances. Third, the study was relatively small; therefore, the findings require confirmation in larger-scale epidemiological studies.

Conclusion

We have shown that MS and its components hyperglycemia and overweight are independently associated with the development of BP. Therefore, clinicians should screen for MS in patients with BP, especially in those who are older, present less erythema, or have high serum C3 concentrations.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (Number: S-K1853) and written informed consent was obtained from all the participants.

Consent for publication

Not applicable.

Author contributions

Bingjie Zhang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft.

Xinyi Chen: Data curation; Investigation; Writing – original draft.

Yangchun Liu: Data curation; Investigation; Writing – original draft.

Fangyuan Chen: Data curation; Investigation; Writing – original draft.

Nan Yang: Conceptualization; Resources; Writing – review & editing.

Li Li: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author on reasonable request.

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