FREQUENCY OF DIABETES MELLITUS IN PATIENTS WITH IMMUNO-BULLOUS DISORDERS

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ABSTRACT

Introduction: Immunobullous disorders (IBDs) are marked by blistering lesions that affect the skin and mucosal surfaces. They are caused by antibody-mediated immune reactions that target structural parts of the skin. A major metabolic disease that is frequently linked to immunobullous diseases is type 2 diabetes mellitus.

Objectives: To determine the frequency of type 2 diabetes mellitus in patients with immunobullous disorders

Methods and patients: The study was conducted in the dermatology department, Khyber Teaching Hospital, Peshawar from July 30, 2021 to January 30, 2022. After taking full history and physical examination, patients with IBD aged 20 to 80 years were screened for type 2 diabetes mellitus, defined as a random blood glucose level of over 200 mg/dl. The test was done using Micro Lab 300 of Vital Scientific using Glucose; GOD-PAP of Dialab. All data were analyzed by SPSS 22. Post stratification Chi-square test was used to determine the association of duration of IBDs and use of systemic steroids with the presence of diabetes mellitus.

Results: Among these 152 patients, 59.2% were female. The mean age was 47.77 years ± 14.30 SD and duration of the disease was 3.12 years ± 1.76 SD. The frequency of diabetes mellitus was 23.7%. Diabetes mellitus was significantly more prevalent in patients with disease duration of more than three years (46.7% versus 8.7%, p = **0.001**) and in those with a history of use of systemic steroids for the IBDs (39% versus 10%, p = **0.001**).

Conclusion: The frequency of type 2 diabetes mellitus was 23.7% among patients with IBDs. Earlier detection of type 2 diabetes mellitus can prevent the associated complication of the disease including the morbidity and mortality**.**

Keywords: Immunobullous disorders, diabetes mellitus, blistering condition

Abbreviations used: IBDs: Immunobullous disorders; **DM:** Diabetes mellitus; **PV**: Pemphigus vulgaris; **BP**: Bullous pemphigoid; **DH**: Dermatitis-herpetiformis; **CLD**: chronic liver diseases; **CKD**: Chronic kidney disease

INTRODUCTION

Immunobullous disorders (IBDs) cause blistering eruption of skin and mucosal surfaces due to antibody-mediated immune reactions against skin structure [1]. IBD incidence rates are 14.5–20.4/million [2,3]. These disorders are long-lasting with high mortality[3].

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The classification of IBDs is based on autoantibodies against target proteins such as desmosomes (pemphigus group), hemidesmosomes and basement membrane (pemphigoid), and tissue-type and epidermal transglutaminase (dermatitis herpetiformis)[4].
Pemphigus, the most common IBD; has increased from 0.1 to 3.32 cases per 10,0000 in the recent past [5]. Pemphigus vulgaris (PV) is the most frequent type of pemphigus, followed by foliaceous. Bullous pemphigoid (BP) is the pemphigoid prototype. Annual BP cases range from 2.5 to 13 per million [6]. In the past decade, the incidence of BP has climbed 1.67-fold [7].
Gluten intolerance causes blistering disorder called dermatitis-herpetiformis (DH) that results in enteropathies [8]. It is commonly found in adults [8]. Anti-endomysial and anti-tissue transglutaminases are found in 10% of DH patients [9]. Thyroid, haematological, and neurological problems are common co-

morbidities of IBDs. Immunofluorescence (IF) is the preferred investigation for IBDs [10].

The prevalence of diabetes mellitus (DM) ranges from 13.1 to 26% in Pakistan[11]. IBD patients utilise high-dose systemic steroids for a long time. By affecting glucose metabolism, systemic corticosteroids increase the risk of diabetes in IBD patients. Data show that diabetes mellitus prevalence is much higher in the Bullous pemphigoid group (24/34 vs 13/556; p <0.001)[12]. Similarly, data reveal that 29.7% and 26.3% prevalence of diabetes mellitus was reported in any form of pemphigus and PV respectively [13].

This study aimed to evaluate the frequency of type 2 diabetes mellitus in local IBD patients which will help the local authorities in updating local data on the topic. This study may provide a platform for future researchers in this regard.

MATERIAL AND METHODS

This retrospective descriptive cross-sectional study was conducted in the dermatology department of Khyber Teaching Hospital, Peshawar, Pakistan, from July 30, 2021 to January 30, 2022. The hospital ethical and research committee granted approval for conducting the study (No. 145/DME/KMC: dated 13/2/025). A total of 152 patients were taken. This study used 26.3% diabetes prevalence in pemphigus vulgaris to compute the sample size [13]. The WHO algorithm was used to calculate this sample size with 95% confidence level and 7% margin of error. All biopsy-proven IBD patients (incisional biopsy taken along with attached bullas) aged 20–80 were enrolled using stratified consecutive sampling. Diabetic patients (both type 1 and type 2), patients with chronic liver diseases (CLD), chronic kidney diseases (CKD), Cushing syndrome, acromegaly, pregnant women, and patients using systemic corticosteroids for any other autoimmune disorder before the onset of the IBD were excluded from the study as systemic glucocorticoids increase insulin resistance and result in iatrogenic diabetes mellitus. All patients gave written informed consent and had a thorough dermatological assessment. The patient's body mass index (BMI), disease duration and duration of use of systemic steroids for the IBD were recorded. A phlebotomist was called and 2ml of venous blood was drawn for random blood sugar testing. The test was done using Micro Lab 300 of Vital Scientific using Glucose; GOD-PAP of Dialab. A random blood glucose level of over 200 mg/dl was used to diagnose diabetes mellitus [14]. Study bias and confounding factors were excluded using strict exclusion criteria. Data were recorded and analysed with SPSS 22. The mean and standard deviation were determined for numerical variables. For categorical variables, frequencies and percentages were determined. Statistical significance was defined as $p<0.05$. For comparison, chi-square test, and student t-test were used.

RESULTS

A total of 152 patients were included in the study. All the patients were biopsy proven. Among these patients, 36 patients (23.7%) were found to have diabetes mellitus. The basic demographic characteristics of the patients are given in Table 1. The duration of IBD and the duration of use of systemic steroids has clinical relevance as systemic steroids taken for longer duration put the patients at risk of developing type 2 diabetes mellitus [13].

Table 1. Demographic characteristics of patients (n=152)

Variables	**Mean ± SD / No. (%)**
Age, (years)	47.77 ± 14.30
Disease duration, (years)	3.12 ± 1.76
Duration of use of steroids, (years)	2.73 ± 1.52
Gender, No. (%)	
Male	62 (40.8 %)
Female	90 (59.2 %)
Autoimmune bullous disorder, No. (%)	
Pemphigus	112 (73.7%)

Pemphigoid group	28 (18.4%)
Tissue type and epidermal transglutaminase group	12 (7.9%)
Diabetes Mellitus, No. (%)	
Yes	36 (23.7%)
No	116 (76.3%)

In subgroup analysis, the frequency of type 2 diabetes mellitus was significantly higher among patients with a disease duration of more than three years (46.7% versus 8.7%, p = 0.001) and among patients with a history of use of systemic steroids for the IBDs (39% versus 10%, p = 0.001). (Table 2)

Table 2: Stratification of diabetes mellitus by disease duration and use of systemic steroids

Variables		**Diabetes Mellitus (n=152)**		**P-value***
		Yes	**No**	
Disease duration	<3 years	8 (8.7%)	84 (91.3%)	0.001
	>3 years	28 (46.7%)	32 (53.3%)	
Use of systemic steroids	No	7 (10%)	71 (90%)	0.001
	Yes	29 (39%)	45 (71%)	

*Chi-square test

DISCUSSION

IBDs are heterogeneous group of mucocutaneous disorders that consist of tissue-bound and circulating autoantibodies against epidermal and dermal adhesive molecules and manifest clinically as bullae and upon rupturing leave behind erosions [15]. These chronic disorders cause high morbidity and mortality [16]. Among the clinical types of IBDs, pemphigus is the most common clinical type, followed by bullous pemphigoid. While dermatitis herpetiformis, which represents the tissue-type and epidermal transglutaminase group, is the least common variant [2,4]. Most cases of pemphigus are pemphigus vulgaris, which accounts for 70% of cases [17]. It is more common in India, Europe, and the US while pemphigus foliaceous, the second most common type, is common in Africa and Brazil [18]. The incidence of bullous pemphigoid rose 17% year from 1996 to 2006 [19]. Above 60, the incidence of BP doubles [20]. Systemic steroids are the major treatment for immunobullous disorders, while DH classically responds to dapsone [21,22]. High doses of systemic steroids can cause metabolic issues, hypertension, secondary diabetes mellitus, Cushing's syndrome, and osteoporosis that leads to fractures [23]. Thus, critical care for such patients must be multidisciplinary. Type 2 diabetes mellitus frequency in IBD patients was investigated in this study.

In our study, the mean age was 47.77 years and a standard deviation of 14.30 years. Disease duration averaged 3.12 years with a standard deviation of 1.76 years. Participants were mostly women (59.2%). The majority of patients (48% across three groups) were 41–60 years of age. Pemphigus was the most frequent IBD type at 73.4%, followed by pemphigoid (18.4%). The least prevalent form was dermatitis herpetiformis, being noted in 7.9% of cases. The mean random blood sugar level was 141.52 mg/dl with a standard deviation of 76.48. Among these 152 patients, 23.7% had diabetes. A significant difference was noted between diabetics and non-diabetics (270.61 mg/dl ± 45.51 SD vs 101.45 mg/dl ± 14.59 SD, p<0.001) in their blood sugar levels.

In our study, the majority of participants were women (59.2%). Siddig O et al. found that females were most likely to have immunobullous disorders in Sudan, which is consistent with our data [19]. Patients with pemphigus made up 73.4% of our study. Among them, pemphigus vulgar was accounted for 80.4% of cases. Pemphigus vulgaris accounts for over 70% of all IBDs worldwide [24]. Our study confirms the widespread incidence of PV in pemphigus. DH prevalence was 7.9% in our study. The literature reports 2.5%–50% DH prevalence globally [25], which is also consistent with the data of our study.

Our study concluded 23.7% prevalence of type 2 diabetes mellitus in patients with IBDs. Hsu Dyt et al. found 26.3% prevalence of DM at any stage of pemphigus, which matches our data [13]. In their study, Johal JS et al concludes 12 to 35% prevalence of diabetes mellitus in

patients with IBDs, which is also consistent with the findings of our study [26]. Dănescu AS et al. found 22.62% of pemphigus vulgaris patients had diabetes mellitus, which correlates with the results of study [27].

In our study, there was a statistically significant difference in blood sugar levels of diabetic patients compared to non-diabetics in IBDs (270.61 mg/dl ± 45.51 SD versus 101.45 mg/dl ± 14.59 SD, p<0.001). According to literature, the bullous pemphigoid group had considerably higher blood sugar levels than the control group (70% vs 12.3%, p<0.0001), which is consistent with our data [12].

In our study, a longer duration of use of steroids was a significantly important factor for diabetes mellitus (39% DM in disease duration >3 yr versus 10% in disease duration <2 yr, p<0.001). Dănescu AS et al. concluded in their study patients suffering from immunobullous disorders taking systemic corticosteroids are at higher risk of diabetes mellitus than others [27].

This study concludes 23.7% frequency of type 2 diabetes mellitus in patients with IBDs. Certain factors such as high doses of systemic steroids and prolonged duration of treatment put these patients at risk of developing diabetes mellitus. In these situations, the main priorities are early detection of the condition and preventing related consequences from diabetes mellitus. And in future, safety of high doses of systemic steroids must be the focus of researchers in patients with IBDs. The limitations of the study are small sample size and patients included are those visiting to a single tertiary care hospital of province. In future similar study should be conducted at larger scale including dermatology units of other tertiary care hospitals of the province.

CONCLUSION

This study concludes that the frequency of type 2 diabetes mellitus in patients with IBDs was 23.7%. Pemphigus group is the most common prevalent disorder among them while dermatitis herpetiformis is the least common variant. Type 2 diabetes mellitus is an unnoticed complication associated with the disease. Certain factors that can predispose these patients to develop diabetes mellitus are the longer duration of IBDs as well as the systemic use of a steroid for a prolonged period. Earlier detection of type 2 diabetes mellitus can prevent the associated complication of the disease and thus timely intervention can minimize the associated morbidity and mortality.

RECOMMENDATIONS

Studies with large sample size and multi centered are recommended to further evaluate the important clinical correlation of diabetes mellitus with IBDs. Thus, it is also recommended that such patients should be regularly screened for diabetes mellitus.

CONFLICT OF INTEREST: Nil

POTENTIAL COMPETING INTERESTS: Nil

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