Assessment of the Prevalence and Risk Factors Associated With Glucocorticoid-Induced Diabetes Mellitus in Pemphigus Vulgaris Patients

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Abstract- Pemphigus vulgaris is a chronic autoimmune disease and glucocorticoids are one of the main treatments. Our study investigates the prevalence and associated factors of glucocorticoid-induced diabetes mellitus in these patients under different glucocorticoid regimens. 36 patients with first diagnosed Pemphigus vulgaris based on pathological and direct immunofluorescence findings who had received different glucocorticoid regimens (1-2 mg/kg oral or 1-2 mg/kg oral with 1g methylprednisolone pulse daily for 3 consecutive days with or without azathioprine) were evaluated during 2014-2016. Our study found that 22.2% of patients had impaired fasting glucose and incidence of corticosteroid-induced diabetes mellitus was 22.2% with no difference between oral and pulse therapy of corticosteroid. The first day after pulse therapy 19 patients of 21 had post bolus hyperglycemia that 36% of them became diabetic after 8 weeks. None of the variables, including age, BMI, HbA1c, LDL, HDL, TG, cholesterol, family history and blood pressure were associated with diabetes. Pretreatment FBS was the factor that would increase the likelihood of glucocorticoid-induced diabetes mellitus, 42.2% of patients with pretreatment FBS 100-126 developed diabetes in comparison with 17.2% in normal pretreatment FBS. Although the group who received azathioprine was associated with increased incidence of diabetes, the overall corticosteroid dose in this group was significantly higher than the other group (P=0.012), and controversy with other studies could be because of difference in corticosteroid dosage and small number of patients. The incidence of diabetes was not different between the group with glucocorticoid pulses and oral prednisolone without pulse therapy. Higher pretreatment FBS can be related to increased incidence of diabetes, but results from this study due to small number of patients are preliminary and multicenter studies are needed.

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Keywords: Glucocorticoid; Diabetes mellitus; Pemphigus vulgaris

Introduction

Pemphigus vulgaris is a rare chronic autoimmune blistering disease affecting the skin and mucosal surfaces which are mediated by circulating antibodies against a protein called Desmoglein 3 on the cell surface of keratinocytes. Clinically all patients with Pemphigus vulgaris have painful mucosal erosions, cutaneous erosions and blisters are also seen in more than 50% of patients. The histologic changes include acantholysis with intraepidermal blisters due to loss of cell-cell adhesion of keratinocytes and deposits of IgG antibodies indirect immunofluorescence.

Pemphigus affects people of all races and cultures. Men and women both get pemphigus at the same rate. It is most common in middle-aged and older adults, but it can occur in young adults and children (1). Prevalence of pemphigus is 0.076 to 1.6 in 100,000. Before the advent of systemic corticosteroids, Pemphigus vulgaris was usually a fatal disease with 50% mortality in 2 years because large areas of the skin lost their epidermal barrier function, leading to the loss of fluids or to secondary infections (2,3). The introduction of systemic corticosteroids and immunosuppressive agents has greatly improved the prognosis of pemphigus; however, the morbidity, and occasional mortality are still significant due to complications of therapy. Diabetes mellitus is one of the major complications, which occur

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because of impaired glucose metabolism by corticosteroids due to increased insulin resistance in tissues, increased glucose production in the liver and impaired glucose consumption in muscles and adipose cells. Diabetes is one of the predisposing factors of mortality in these patients (4,5). Up to 50% of patients have increased insulin resistance in various studies and prevalence of corticosteroid-induced hyperglycemia is 12.6% to 40% depending on different factors such as dose, duration of therapy and route of administration (6,7,8,9, and 10). Immunosuppressive agents such as azathioprine, mycophenolate mofetil, and cyclosporine are often used. Azathioprine is used at a dose of 2-4 mg/kg (usually 100-300 mg/day), and its common side effects are nausea and dose-dependent myelosuppression (11).

The aim of our study is to determine the incidence of glucocorticoid-induced hyperglycemia and associated possible risk factors (age, sex, HDL, LDL, TG, cholesterol, HbA1c, blood pressure, family history and type of adjuvant) in different corticosteroid regimens in order to prevent from incidence or complications in these patients. In this study we compare the incidence of diabetes between oral and pulse prednisolone, and also we investigate post-bolus hyperglycemia by measuring FBS levels after every pulse therapy.

Materials and Methods

In this cross-sectional study, all patients with first diagnosed Pemphigus vulgaris according to the pathological and immunological tests (direct immunofluorescence) referred to the Departments of Dermatology of Razi Hospital at Guilan province, north of Iran, from March 2014 through March 2016. At first, all patients after admission (first hospitalization for Pemphigus vulgaris) underwent a precise assessment including basic tests (FBS, HbA1C, Cholesterol, TG, HDL, and LDL), Blood pressure measurement (measured in the supine position and from left hand after 30 minutes rest), and height and weight measurement. Demographic data such as age, sex, past medical history and diabetic risk factors were extracted from the questionnaire. All participants signed an informed consent. Patients were categorized into four groups according to the type of the therapy. Group A and B received oral prednisolone 1-2 mg/kg daily without and with 100 mg azathioprine respectively. Group C and D underwent methylprednisolone pulse therapy 1000 mg daily for 3 consecutive days plus 60mg oral prednisolone without and with 100 mg azathioprine respectively (Table 1). Patients with known diabetes mellitus or FBS more than 126 mg/dl or HbA1c more than 6.5% before pemphigus treatment, previous prednisolone therapy for more than 7 days in the last two years and Patients without pathological confirmation of Pemphigus vulgaris were excluded from the study. FBS was checked after every pulse therapy and then 2 times a week and patients were evaluated for 8 weeks and patients were divided into diabetic and non-diabetic groups.

Table 1. Therapeutic regimes in treatment groups

	A	B	C	D
Oral prednisolone without pulse therapy (1-2 mg/kg/day)	+	+	--	--
Azathioprine (100 mg/d)	-	+	-	+
Oral prednisolone with methylprednisolone, Pulse Therapy. (1000 mg/day * 3day)	-	-	+	+
Patients number	5	4	9	18
Follow up duration (week)	8	8	8	8
Patients number with the second pulse	--	--	3	8
Total numbers of pulses	--	--	12	26

The statistical analysis of all data was performed using SPSS version 19. The prevalence of diabetes mellitus was calculated. All quantitative data were expressed as mean and standard deviation. For comparative analysis, we used Student's *t*-test and the X2 test depending on the variable. Correlations between quantitative variables were made with Pearson's correlation coefficient, and for comparing the groups, ANOVA was used. *P* less than 0.05 were considered significant.

Results

Forty-two Pemphigus vulgaris patients were admitted at the hospital during study time. 4 of them excluded from the study because of previous corticosteroid usage and 2 patients left the study. The remaining 36 patients were divided into 4 groups. There were 5 patients in group A, 4 patients in group B, 9 patients in group C and 18 patients in group D. 3 patients in group C and 8 patients in group D underwent second pulse therapy after 21-30 days from the first one (See Table 1).

Gender distribution was 17 women (47.2%) and 19 male (52.8%). The mean time of admission was 23 days. Because the period of study was eight weeks, the follow-up was done on an outpatient basis on Patients who were discharged earlier. The average age was 48±15 years. BMI in 58.3% of patients was in normal range, and overweight was found in 30.6% and obesity in 8.3% and morbid obesity in 2.8% of patients. A family history of diabetes mellitus was found in 30.6%.

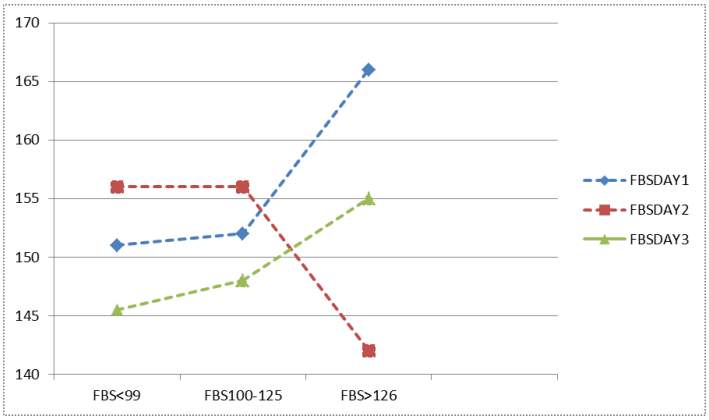
The baseline LDL and HDL levels were 118±44 mg/dl and 41±8 mg/dl respectively. Increased level of LDL was found in 61.1% of patients. The baseline TG and cholesterol levels were 119±47mg/dl and 181±35 respectively. Increased level of TG and cholesterol were seen in 36% and 25% of patients. 58.3% of patients had normal blood pressure.

A day after each pulse of methylprednisolone, glucose levels increased to 155±28 mg/dl, 152±24 mg/dl, 148±30 mg/dl respectively (increased significantly compared to the FBS level before treatment) but none of them were significantly different between group C and D (Table 2). 19 patients of 21 patients underwent pulse therapy had hyperglycemia after the first pulse that 7 of them (36%) became diabetic after eight weeks. In our study, the patients who had higher FBS level at first and third day; their FBS level was also high after 8 weeks, but it was not true about the second day FBS level (Graph1).

Table 2. Mean FBS levels a day after each pulse therapy in C and D groups

*	Mean	Standard deviation	*P*	Lower confidence interval	Upper confidence interval
FBS 1st day(mg/dl)	C:152.90 D:157.24	C:23.269 D:30.363	0.701	-23.679	24.714
FBS 2nd day(mg/dl)	C:157.80 D:149.41	C:22.695 D:25.742	0.402	-17.686	19.651
FBS 3rd day(mg/dl)	C:150.70 D:147.24	C:32.469 D:30.667	0.784	-27.968	29.086

* FBS mean difference after the First, second and third days of pulse between the two groups, C (treated with methylprednisolone pulse then oral prednisolone) and D (treated with methylprednisolone pulse then oral prednisolone and azathioprine), is investigated



Graph 1. Relationship of FBS levels after every pulse with FBS level after 8 weeks

8 weeks after treatment; 55.5%of patients were non-diabetic, 8 patients (22.2%) were pre-diabetic (2 patients in group A and 1 patient in group C and 5 patients in group D), and 8 patients (22.2%) were diabetic (1 patient in group B and 7 patients in group D). Our study showed that administration of corticosteroids significantly increases incidence if diabetes (*P*=0.034). Pretreatment FBS was a strong predictor of

corticosteroid-induced diabetes. 17.2% of patients with pretreatment FBS fewer than 100 became diabetic (42.2% in patients with pretreatment FBS 100-126) and 17.2% of them developed impaired glucose intolerance (42.2% in patients with pretreatment FBS 100-126) (*P*=0.05).

After 8 weeks the mean FBS level was only significantly different between group C and D (*P*=0.012) and the relationship between high FBS level and adjunction of azathioprine to pulse therapy was seen (*P*=0.009). As there was no difference in FBS levels after every pulse therapy between group C and D, we evaluated maintenance glucocorticoid dosage during 8 weeks, and we found that group D had taken significantly higher (up to 20 mg in some patients) glucocorticoid dose than group C (0.012). There was no difference in FBS level according to number of pulses (*P*=0.866).

The mean HbA1c level in the non-diabetic group was 4.76 and in pre-diabetic and diabetic groups was 5.04 and 5.16 respectively, and there was no difference in HbA1c level between these groups (*P*=0.219). Mean levels of LDL (116.85 in non-diabetic, 130 in pre-diabetic and 109.88 in diabetic), HDL (42.65 in non-diabetic, 37.38 in pre-diabetic and 40.63 in diabetic), TG (115.05 in non-diabetic, 119.63 in pre-diabetic and 128.38 in diabetic), and cholesterol (184.90 in non-diabetic, 172.38 in pre-diabetic and 182.38 in diabetic), were not significantly different between non-diabetic and diabetic patients (Table 3). Family history (*P*=0.225), BMI (*P*=0.403) and blood pressure (*P*=0.072) showed no association with incidence of diabetes.

Table 3. Association between variables and incidence of diabetes

Dependent Variable	(I) FBS	(J) FBS	*P*	95% Confidence Interval	
				Lower Bound	Upper Bound
HD	100-125	<99	0.225	-13.07	2.52
	>126	<99	0.787	-9.82	5.77
LDL	100-125	<99	0.732	-31.03	57.33
	>126	<99	0.915	-51.15	37.2
CHOLE	100-125	<99	0.637	-47.35	22.3
	>126	<99	0.981	-37.35	32.3
TG	100-125	<99	0.967	-42.97	52.12
	>126	<99	0.758	-34.22	60.87
Age	100-125	<99	0.620	-44.24	23.43
	>126	<99	0.840	-33.2	29.98
Sex	100-125	<99	0.224	-13.12	10.45
	>126	<99	0.437	-18.35	14.77
BMI	100-125	<99	0.403	-35.55	16.67
	>126	<99	0.688	-46.11	23.11
BP	100-125	<99	0.0702	-1.233	2.33
	>126	<99	0.0801	-1.33	2.16
FH	100-125	<99	0.225	-13.06	2.54
	>126	<99	0.488	-14.01	11.02
HbA1c	100-125	<99	0.219	-12.89	3.34
	>126	<99	0.413	-14.33	12.22
Pulse or oral	100-125	<99	0.879	-45.32	54.89
	>126	<99	0.923	-48.99	48.23
Azathioprine	100-125	<99	0.009	-1.21	2.12
	>126	<99	0.009	-1.23	2.13
Pulse number	100-125	<99	0.866	-56.35	34.78
	>126	<99	0.899	-59.33	31.98
Pretreatment FBS	100-125	<99	0.050	-3.42	2.33
	>126	<99	0.050	-3.43	2.11

By performing Pearson's correlation between the type of therapy and other risk factors, we found that none of them was statistically predictive factor in the incidence of diabetes mellitus. But the positive correlation between azathioprine and corticosteroid dosage was seen (Table 4).

Table 4. Correlation between risk factors and type of therapy (with or without Azathioprine)

Therapy	HDL	TG	CHOLE	HbA1c	BP	BMI	FH	Corticoid dose
Pearson correlation	-0.331	0.061	-0.166	0.301	0.195	0.286	0.145	0.595
P	0.069	0.722	0.334	0.075	0.255	0.091	0.277	0.050

Discussion

In spite of effectiveness of corticosteroids in the treatment of patients with Pemphigus vulgaris, development of severe side effects like diabetes has limited their use. Our study on 36 patients with Pemphigus vulgaris, who underwent different regimens of corticosteroid therapy (oral or pulse therapy) with or without azathioprine showed that 22.2% of patients had impaired fasting glucose and incidence of corticosteroid-induced diabetes mellitus were 22.2% with no difference between oral and pulse therapy of corticosteroid. Other studies had similar results, Valikhani *et al*., reported that the incidence of corticosteroid-induced diabetes mellitus was 27.9% among Pemphigus vulgaris patients (12). Generally, the rate of corticosteroid-induced hyperglycemia was 30-40% in the majority of studies (13,14).

In this study, we found a significant increase in post bolus glucose level, more evident after the first pulse with the elevation of about 50 mg/dl. 81% of patients after the first pulse, 96% after the second pulse and 96% after the third pulse had hyperglycemia. Perez *et al*. reported similar elevation of glucose level after the first pulse (40 mg/dl) and some different from our study, 68% of patients after the first pulse, 94% after the second pulse and 98% after the third pulse had hyperglycemia (15).

In our study mean level of blood glucose after pulse therapy was not different according to adjunction of azathioprine but at the end of treatment a significant difference was seen at the rate of developing diabetes mellitus between groups with and without azathioprine (0% in pulse therapy without azathioprine compared to 25% in the opposite group). As patients underwent azathioprine therapy had taken significantly higher dose of maintenance glucocorticoid (average level of corticosteroid: 63.8 mg/dl in group D and 59.98 mg/dl in group C), we can assume that the difference in the rate of diabetes between group C and D may be related to small number of patients in our study or the different maintenance doses of glucocorticoid between dose groups not to the adjunction of azathioprine (Table 4). Almost other studies had shown that azathioprine had a preventive effect on the onset of diabetes mellitus and no study was found in the relationship of azathioprine and increased risk of diabetes mellitus (16,17). In contrast to azathioprine, a study found relationship between administration of mycophenolate mofetil and increased incidence of diabetes mellitus (18). In this study pretreatment FBS was the factor that would increase the likelihood of glucocorticoid-induced diabetes mellitus, 42.2% of patients with pretreatment FBS 100-126 developed diabetes in comparison with 17.2% in normal pretreatment FBS.

Type of therapy, age, BMI, family history, HbA1C, LDL, HDL, TG, and cholesterol were not associated with diabetes. Valikhani *et al*. found that HbA1c (mean level of 5.4 in diabetic patients compared to 4.98 in non-diabetic) and triglyceride (159mg/dl in diabetic patients compared to 120 in non-diabetic) were risk factors for developing diabetes (12). But Alavi *et al*. reported similar findings in our study and in their study age and BMI and family history were not associated with hyperglycemia, and glucocorticoid dose and duration of treatment were the only effective factors for developing diabetes (14). There was also another study by Esmaeili *et al*., in which age, BMI, HbA1c, and HDL were strong risk factors for developing diabetes (19). Although we found no association between age and diabetes, we should consider that average age was under 50 years in our study and it may influence the association between age and diabetes. About the lack of association between family history and diabetes, it is possible that screening for diabetes is not complete in Iranian families. Results from this study due to small number of patients are preliminary, Due to the rarity of pemphigus in the world in order to investigate incidence of diabetes according to different corticosteroid regimens performing multicenter studies is recommended.

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