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# Risk Factors of Glucocorticoid-Induced Diabetes Mellitus in Systemic Lupus Erythematosus

Mojdeh Zabihi Yeganeh, Saeideh Sadeghi✉

Department of Internal medicine, Firoozgar Hospital, Iran University of Medical sciences, Tehran, Iran

**Abstract**

**Background:** The aim of this study was to investigate the prevalence and associated factors of glucocorticoid-induced Diabetes mellitus (GIDM) in patients with systemic lupus erythematosus (SLE) under glucocorticoid therapy.**Martials and Methods:** Patients with SLE who had received high-dose glucocorticoid therapy (prednisolone≥1 mg/kg/day) at Rasoul Akram and Firoozgar hospitals were recruited during 2006-2011.**Results:** A total of 81 patients with SLE were evaluated. 21 patients (25.9%) of them developed GIDM after high-dose glucocorticoid therapy. Univariate analysis of data showed that old age, family history of diabetes mellitus (DM) and use of Mycophenolate mofetil were factors that would increase the likelihood of GIDM.**Conclusion:** In summary, GIDM was developed among 25.9% of patients with SLE after high-dose glucocorticoid therapy. Old age, family history of DM and use of Mycophenolate mofetil were determined to be factors responsible for increasing the risk of developing GIDM. **[GMJ. 2013;2(2):39-43]**

**Keywords:** Diabetes Mellitus; Glucocorticoid; Systemic Lupus Erythematosus; Risk factor

## Introduction

Systemic Lupus Erythematosus (SLE) is one of the most prevalent autoimmune diseases which are characterized with diffuse damage of cells and tissues by immune mediators and pathways by anti-nuclear antibodies. In other words, SLE is a chronic, idiopathic, inflammatory and multi-systemic disorder which can present with renal, musculoskeletal, cardiopulmonary, neurologic, and hematologic signs and symptoms [1-3]. Results have shown that classic pathway of the complements are the main cause of this disease, while their normal activity is to eliminate foreign immune complexes. This will result in non-eliminated immune complexes deposition in other organs such as kidneys; which can induce damage by the complements [4]. Choosing an appropriate treating program in these patients relies on the severity, recurrence, and the complications of the disease itself and the used drugs, as systemic glucocorticoids are one of the most respectful members of the treatment package [5,6]. However, any patient receiving these drugs is prone to glucose intolerance and diabetes. In fact, glucocorticoids can induce intra and extra hepatic insulin resistance; as then can reduce glucose transport into fat cells and myocytes and induces apoptosis in pancreas's

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Fax: +98 731 2227091
PO Box 7461686688
Email:info@gmj.ir

✉ **Correspondence to:**
Saeideh Sadeghi, Resident of Internal medicine,
Department of Internal medicine, Firoozgar Hospital,
Iran University of Medical Sciences, Tehran, Iran
Telephone Number: -
Email Address :m-zabibi@tums.ac.ir

beta cells which can result in reduced insulin secretion [7]; furthermore, glucocorticoids can reduce GLUT-2 expression and increase in appetite and therefore, result in obesity [8]. All of these theories are assumed to be transient and only at the time of glucocorticoid consumption; however, studies have shown that risk of diabetes, obesity, and therefore risk of cardiovascular and microvascular complications increases in patients with long term use[8-10]. As the number of studies regarding this issue is limited in the Middle East, and increasing prevalence of SLE patients and use of glucocorticoid in our country, the aim of this study is to determine the risk factors of GIDM in SLE patents.

## Martials and Methods

### *Subjects*

In this cross-sectional study, all patients with documented SLE referred to rheumatology ward of Rasoul-e-Akram and Firoozgar Hospital in the time period between 2006 and 2011 were included in our study. All patients were under treatment with high dose glucocorticoids (equivalent to more than 1mg/kg/day with or without IV 1000 mg methyl prednisolone cycle pulse in 3 consecutive days). Patients with known diabetes mellitus before SLE treatment (based on ADA criteria, 2003), fasting blood glucose (FBS) more than 126 mg/dl, less than 4 week simultaneous treatment and pregnant women were excluded from the study.

FBS was evaluated 2-3 times after starting the SLE treatment. All patients were admitted for at least 2 weeks. FBS was checked in every out-patients clinic follow-up session. Demographic factors such as age, sex, smoking, etc., clinical findings of vital organs such as central nervous, renal, and urinary systems and the indications of high dose glucocorticoid prescription (hemolytic anemia, thrombocytopenia, vasculitis, etc.) history of hypertension and dyslipidemia, body mass index, and familial history of SLE and Diabetes were extracted from their electronic medical files and entered into a checklist. Other medication information such as duration and dosage of corticosteroids, other immunomodulation drugs (Cyclosporin, Cyclophosphamide, Azathioprin, Hydroxy-Chloroquin, mycofenolate mofetil, etc.) were also included. At the end, all patients were evaluated for GIDM and divided into diabetic and non-diabetic groups.

All enrolled patients were informed about the study and they were able to decide regarding participation and a written consent was obtained. The patients were not charged by additional fees for the drugs of any step of this study. All information was kept confidential and all authors were bind into Helsinki declaration codes.

### *Statistical analysis*

The data were evaluated and analyzed by SPSS version 19 (SPSS Inc., Illinois, USA). All quantitative data are expressed as mean ± SD. For comparing the groups ANOVA and repeated measurements were used as for parametric and non-parametric data, evaluated by Kolmogorov-Smearnov test. P less than 0.05 were considered as significant.

## Results

### *Demographic data*

At the end of our survey, 81 patients fill the criteria and were evaluated. The male to female ratio was 15/66 and mean age was 37±14 (range 14-76) years and mean BMI was 25.9±3 kg/m2. From all patients, 27 (33.3%) had hypertension. Five (6.1%) patients had history of smoking; 14 (15.7%) had familial history of diabetes. Renal and CNS involvement was seen in 29 (35.8%) and 6 (7.4%) patients; other patients had other organ involvements. Other information is demonstrated in table 1.

Figure 1 demonstrates daily dose of steroids. As seen, 60 and 50 mg were the highest prescription doses, respectively. The mean dose was 56±10 mg. The mean duration of corticosteroid therapy was 38.4±12.8 days

### GIDM

At the end of our survey, 21 (25.9%) patients were diagnosed by GIDM. Table 1 demonstrated all demographic information divided by the two groups; as seen, age and familial history of diabetes were significantly different between diabetic and non-diabetic SLE

patients. Other parameters did not have any significant difference. Table 2 shows the usage of other drugs among corticosteroid and as demonstrated, Mycophenolate mofetil usage was significantly higher in Diabetic patients.
Backward stepwise Logistic Regression modeling (Wald) is described in table 3. All three parameters could independently predict diabetes in our patients.

**Table-1.** Demographic data of the patients and both groups

| | Total | GIDM | Non-GIDM |
|---|---|---|---|
| Age (year) | 37±14 | 47±13.7 | 32.5±13.6 |
| Sex (M/F) | 15/66 | 3//18 | 12//48 |
| Renal Involvement-N (%) | 29 (35%) | 8 (38.1%) | 21 (35%) |
| Hypertension- N(%) | 27 (33.3) | 9(42%) | 18 (30%) |
| CNS involvement-N(%) | 6 (7.4%) | - | 6 (10%) |
| Familial history of DM- N (%) | 14 (17.2%) | 10 (47.6%) | 4 (6.6%) |
| Smoking -N (%) | 5 (1.6%) | 2 (9.5%) | 3 (5%) |
| BMI (kg/m2) | 25.9±3 | 26.8±2.2 | 24.8±4.7 |
| HDL (mg/dl) | 45.8±16.7 | 1/19±2/48 | 44.9±15.8 |
| LDL (mg/dl) | 101±46 | 111±52.9 | 98.3±44.3 |
| Total Cholesterol (mg/dl) | 176±67 | 192±72.6 | 170.6±65 |
| Triglyceride (mg/dl) | 177±81 | 197±81.9 | 169±80 |
| Daily dose of Glucocorticoid (mg) | 38.4±12.8 | 49±10.8 | 53±10.3 |
| Glucocorticoid pulse -N (%) | 25 (30.86%) | 7 (28%) | 18 (72%) |

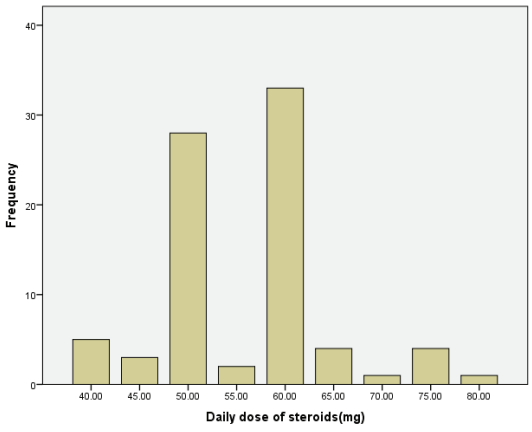


**Figure-1.** Bare chart of daily dose of steroids in our study.

**Table-2.** The use of immunosuppressant drugs in both diabetic and non-diabetic patients

| Drugs | Total | Diabetic | Normal | P-value |
|---|---|---|---|---|
| Cyclosporine | 4 | 1 | 3 | 0.96 |
| Cyclophosphamide | 17 | 5 | 12 | 0.71 |
| Azathioprine | 18 | 5 | 13 | 0.83 |
| Hydroxy Chloroquin | 79 | 21 | 58 | 0.39 |
| Mycofenolate | 25 | 10 | 15 | 0.05 |

**Table-3.** Logistic regression modeling by backward stepwise Method; Diabetes as the independent factor

| | OR | CI 95% | P-value |
|---|---|---|---|
| Age | 1.07 | 1.05-1.15 | 0.02 |
| Diabetes Familial History | 22.72 | 3.9-125 | >0.001 |
| Mycofenolate Use | 5.1 | 1.1-23.25 | 0.035 |

## Discussion

Our study demonstrated the risk factors of diabetes in SLE patients treated with high dose corticosteroids, as 21 out of 81 patients (25.9%) suffered from diabetes. Most of the studies concentrated on GIDM after renal transplantation and mostly evaluated the relation between treatment duration and daily dosage. Jung et al [11] showed 12.6% GIDM and Panthakalam et al [12] founded 8.8% after a mean of 24 months of corticosteroid treatment. As these two studies had different timing and dosage regarding corticosteroids with the present study, the prevalence of GIDM remains similar; however, previous surveys resulted in 1-53%, which is a wide range and can be due to different samples than ours [13-15]. High dose corticosteroids are widely used in end organ involvements. As preserving the implanted kidney is one of the most important concerns in SLE, the dose of corticosteroids is crucial. In those studies, the main risk factors were old age, tacrolimus consumption, familial history of diabetes, Beta blocker consumption, obesity and some specific races [11-15].
Our study demonstrated that higher age and positive familial history of diabetes had an important role in familial history of diabetes. Jung and Panthakalam [11,12] have also demonstrated the same results.

The vitality of the beta cells decreases by age and though, the volume of beta cells will decrease which can result in lower insulin rate and diabetes. Furthermore, corticosteroids can induce diabetes by intra and extra hepatic insulin resistance and other factors such as genetic (for example, HLA-B27) can be considered as a diabetes risk factor, as other immune diseases share the same genetic characteristics [16]. Glucocorticoids can increase appetite and obesity is a known cause of diabetes [7,8]; therefore, there are many pathways which glucocorticoids can result in insulin resistance and diabetes. Since our study was retrospective, we did not have enough information regarding the previous dosage and other risk factors.

The underlying diseases in which corticosteroids are used are usually an inflammatory process due to high production of cytokines. These factors can affect the glucose balance and help other pathophysiological pathways to induce diabetes. Reduced sensitivity of insulin regarding high corticosteroids levels have been shown in several studies. Clore et al [17] have shown that even after discontinuing corticosteroids, the level of plasma insulin increases at the same glucose concentration. Reduced insulin secretion potential in higher corticosteroids doses is another mechanism of insulin resistance. This effect can increase by using cyclosporine or tacrolimus due to induced beta cell apoptosis by blocking pro-survival factors such as NF-KB. In molecular schema, corticosteroids effects are as follow:

Direct pre-receptor and post-receptor action

Indirect increase of glucose by degradation of fatty acids and amino-acids during stress and exogenous corticosteroids [7-9,12-17].

Although there are studies regarding the effect of glucocorticoids on glucose balance and this effect has been known about a century [18,19], several new studies have also linked exogenous corticosteroids pulse in diabetes formation.

Increasing diabetes in patients with Mycophenolate mofetil was one of the odd results of our study. The reason is unknown; however, there are studies demonstrating 12-47% increase in glucose in patients after kidney transplantation [20].

Interpreting the results based on synchronicity of other drugs such as tacrolimus, cyclosporine, and prednisolone, are not that easy. Maybe, Mycophenolate can interfere with insulin secretion [20,21] As is our study, the diagnosis of diabetes were based on FBS, there is a possibility that these drugs may interfere with postprandial glucose. For example, Uzu et al have found 40.5% GIDM in patients with primary renal failure, who all were diagnosed by postprandial hyperglycemia [13].

At the end, we modeled the significantly different factors by logistic regression analysis (Age, Family history of DM, and Mycophenolate mofetil). Other studies have also demonstrated other factors such as duration and dose of corticosteroids. Clore et al [14] have demonstrated an odd's ratio of 1.5-2.5 for corticosteroids in DM, and duration and dose of corticosteroids was significant predictor of GIDM. Zeng et al [15] have also demonstrated that higher age and dose of corticosteroids were the most important factors in predicting the 31.5% GIDM in their study. As our investigation was based on medical files, the information for definite diagnosis of GIDM was impaired. Thus, conducting a prospective study using HbA1c and postprandial glucose can help demonstrating the fact more clearly.

Conclusion

Our study demonstrated the risk factors of GIDM in SLE patients treated with high dose corticosteroids. As shown, 25.9% of the patients resulted in GIDM. Higher age, familial history of DM, and using Mycophenolate mofetil, were found as independent predictors of GIDM in these patients; however, further prospective studies are still recommended.

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**Conflicts of Interest**

Non

## References

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