International Journal of Research in Health Sciences
ISSN: 2321-7251
Published by Atom and Cell Publishers
Available online at: http://www.ijrhs.org/
Original Article

Corticosteroid induced diabetes in systemic lupus erythematosus patients

Rizna Abdul Cader[1], Amy Koo Mei Yin[1], Siti Nurfatin Haron[1], Azrul Reesha Yassin[1], Ismail M Ahmad[1], Rozita Hod[2]

[1]Department of Medicine and [2]Department of Public Health, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Received: 01-02-2017 / Revised Accepted: 21-03-2017 / Published: 24-05-2017

ABSTRACT

Introduction: Corticosteroid induced diabetes mellitus (DM) is a well-recognized complication in SLE patients receiving corticosteroids with a prevalence of 12.6% to 25.9%. **Methods:** Cross-sectional study involving SLE patients attending outpatient clinics between February and July 2014 who developed DM after treatment with corticosteroids. Their demographic data, prescription and laboratory investigations were collated and medical records reviewed. **Results:** 228 patients (207 female, 21 male), aged 40.48 ± 12.86 years with SLE duration of 11.65 ± 6.46 years were recruited. Majority (87%) had lupus nephritis. Their mean BMI was 25.03 ± 5.36 kg/m2. Twenty six (11.4%) patients aged 50.12 ± 11.84 years had corticosteroid induced DM. Their SLE vintage and BMI were 14.38 ± 6.49 years and 22.07 ± 3.24 kg/m^2 respectively. All patients received corticosteroid (7.92 ± 4.83 years) prior to development of DM, with a prednisolone dose of 15.00 ± 9.87 mg/day at diagnosis. Their duration of corticosteroid induced DM was 7.31 ± 6.46 years with HbA1c of 7.19 ± 1.95%. We found diabetics to be older, obese and hypertensive. On multivariate analysis, the main risk factors for corticosteroid induced DM were older age and higher BMI. **Conclusion:** Corticosteroid induced DM is a common complication in SLE patients receiving corticosteroids.

Keywords: complications, corticosteroid induced diabetes mellitus, diabetes mellitus, risk factors, systemic lupus erythematosus

***Address for Correspondence:** Dr Rizna Abdul Cader, Consultant Nephrologist, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia; Rizna_c@hotmail.com

How to Cite this Article: Cader RA, Mei Yin AK, Haron SN, Yassin AR, Ahmad IM, Hod R. Corticosteroid induced diabetes in systemic lupus erythematosus patients. Int J Res Health Sci 2017; 5(1): 1-5.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune, connective tissue disease of unknown aetiology that is characterized by heterogeneous clinical and laboratory features.[1] SLE can affect multiple organs and prognosis depends on the organs involved and severity of disease. The prevalence of SLE in Malaysia has been reported to be 43/100,000 population.[2,3]

Corticosteroids are the mainstay of treatment in SLE and dosage varies with the severity of SLE and organ involved. Corticosteroids decrease pro-inflammatory cytokine synthesis and T-cell function, thereby controlling inflammation and lupus activity.[4,5] However, despite their benefits, administration of corticosteroids may increase the serum glucose in a patient without previously diagnosed glucose intolerance as well as in those who have impaired glucose tolerance or diabetes mellitus (DM).[6] Other adverse effects of corticosteroids include obesity and hypertension. These together with corticosteroid induced DM can increase the risk of SLE patients developing premature coronary artery disease in addition to the chronic inflammation cause by SLE. [7,8]

Although the mechanisms behind corticosteroid induced DM are unclear, increased hepatic gluconeogenesis, inhibition of glucose uptake and metabolism in peripheral tissues and altered insulin action have been postulated.[9] Furthermore, approximately 30% of patients with SLE develop a second or third autoimmune condition like DM. [10] DM is highly prevalent in Malaysian adults with a prevalence of 15.2% and has been projected to rise to 21.6% by 2020.[11] Similarly, the worldwide prevalence of DM is also increasing.

The prevalence of corticosteroid induced DM has been reported to be between 12.6 to 25.9% and varies on the patient population and treatment protocols.[12,13] Most of the reported data comes from transplant patients.[14,15] Corticosteroid induced DM after transplantation is associated with adverse outcomes on organ survival and patient morbidity.[16] We therefore wanted to review the prevalence of corticosteroid induced DM in our SLE patients and the risk factors associated with it.

MATERIALS AND METHODS

Patients: This was a cross sectional study involving all SLE patients attending the nephrology clinic at Universiti Kebangsaan Malaysia Medical Centre. All SLE patients who received treatment with corticosteroids were screened and recruited into the study after informed consent. The screening and enrolling period was from February 2014 to July 2014. This study was approved by the Universiti Kebangsaan Malaysia Medical Centre Ethics & Research Committee (FF-2014-050).

SLE patients are reviewed routinely every 3 to 4 months at our instituition unless clinical status requires more frequent visits and those in long term remission are reviewed on a six monthly basis. At each visit, the patients' urine is tested for glucose, protein and blood. Fasting blood glucose is routinely checked at every outpatient clinic visit. All patients who consented were given two questionnaires. The screening questionnaire was used to collect demographic data and to screen for patients who developed DM after treatment with corticosteroids. Medical records of patients with DM (either from the questionnaire or laboratory investigations), was reviewed to gather more data on DM. The information obtained included the onset of DM (before or after diagnosis of SLE), how DM was diagnosed, family history of DM and compliance to medication. Clinical data such as dose and duration of steroid at the time DM was diagnosed, treatment received and complications of DM were also collected. We also collected data on concurrent use of hydroxychloroquine and other immunosuppressive medications such as cyclosporine A, tacrolimus and mycophenolate mofetil.

Definition of Diabetes Mellitus: The diagnosis of DM was based on the 2010 American Diabetes Association's criteria whereby DM is defined by a fasting plasma glucose of ≥ 7 mmol/L or two hours post prandial glucose of ≥ 11.1 mmol/L, or current use of anti-diabetic agents. [16] Corticosteroid induced DM was defined as a fasting glucose concentration ≥ 7.0 mmol/l or a random glucose concentration ≥ 11.1 mmol/l on two occasions after treatment with high dose corticosteroids (prednisolone ≥ 30mg/day for two weeks or more than two weeks regardless the dose). [16]

Statistical analysis: Data was analyzed using the SPSS version 22.0 (SPSS Inc, Chicago, IL, USA). All data was tested for normality. Normally distributed numerical data are expressed as mean ± standard deviation. Non-normally distributed data are reported as median with interquartile range (IQR).

We used chi–square test to compare between categorical variables between those with and without corticosteroid induced DM and Student's t test to compare continuous variables. We used logistic regression analysis to find the independent predictors of corticosteroid induced DM.

In all tests, a p-value < 0.05 was considered significant. To power the study at 90%, our calculated sample size was 220 patients.

RESULTS

We enrolled a total 228 patients and their demographics and clinical characteristics are shown in Table 1. Twenty six patients (11.4%) with SLE were diagnosed with corticosteroid induced DM. Table 2 shows the comparison between those with and without corticosteroid induced DM. We found that the patients with corticosteroid induced DM were older with a higher BMI. They also had higher systolic blood pressure. The patients with corticosteroid induced DM had higher complement levels. Table 3 shows the demographic and laboratory characteristics of patients with corticosteroid induced DM. Eight patients developed complications of DM such as diabetic nephropathy, diabetic retinopathy, stroke, peripheral neuropathy and cranial nerve palsy. The patients with corticosteroid induced DM had high serum lipid profile.

Of the 26 patients who developed corticosteroid induced DM, 12 were either treated previously or were on a calcineurin inhibitor (CNI) at the time of developing corticosteroid induced DM. However, when we compared those treated with and without CNI, we found no significant risk of developing corticosteroid induced DM with CNI use.

DISCUSSION AND CONCLUSION

Our prevalence of corticosteroid induced DM was similar to the reported literature whereby Kim et al reported a prevalence of 12.6% and Yeganeh et al reported a higher prevalence of 25.9%. [13,17] Both these studies reported in Asian patients who have a higher risk of developing DM compared to their Caucasian counterparts. We believe the reason for the slightly lower prevalence in our patients is the relatively lower doses of corticosteroid used at our institution for the treatment of lupus nephritis.

Risk factors associated with corticosteroid induced DM include cumulative dose and duration of steroids, ethnicity, older age, high BMI and the use of CNI especially tacrolimus. [13, 17,18] Our study revealed that the development of corticosteroid induced DM was significantly associated with older age and consistent with other studies in both SLE and post-transplant patients.[12-15,19] The mean age of our SLE patients that developed corticosteroid induced DM was 50.15 ± 11.84 years and more or less consistent with Yeganeh et al where their mean age was 47.00 ± 13.7 years. [17] As one gets older, not only does the number of beta cells which secrete insulin reduce, but also the beta cell vitality decreases thereby, resulting in lower insulin secretion and predisposing them to DM.[20]

In the general population obesity is a well-recognised risk factor for the development of DM and studies have shown that the threshold BMI for Asians to develop DM is lower than their Caucasian counterparts. We found our patients with corticosteroid induced DM had a higher BMI and studies in post-transplant patients have shown the association between obesity and corticosteroid induced DM .[21-23] It is believed that adiponectin reduces with increasing adiposity and new onset of DM after transplantation has been associated with reduced adiponectin.[24] It is difficult to conclude whether the higher BMI was due to the effects of the corticosteroids or whether these patients were just obese and would have eventually developed DM and the use of corticosteroids hastened the process of them developing DM. However, Simmons et al believe otherwise, and suggested that corticosteroids primarily precipitate diabetes in a group of individuals that otherwise have less risk factors for diabetes.[25]

The development of corticosteroid induced DM in SLE patients has been associated with dose and duration of corticosteroids at the time of diagnosis and family history of diabetes. [13, 26-28] A higher dose and a longer duration of corticosteroids were important factors in contributing to corticosteroid induced DM among SLE patients.[13] Our patients developed corticosteroid induced DM at a higher doses (8.7 ± 4.7 mg/day) compared to Ha et al, (6.0 ± 6.3 mg/day), who demonstrated Koreans were receiving a lower dose of steroids at diagnosis of DM.[12] Furthermore, our patients had been on a longer duration of corticosteroids by the time they developed corticosteroid induced DM compared to Ha et al.[12] The exact mechanism of how corticosteroids raise blood glucose levels has not yet been identified. However, it is believed that corticosteroid increase hepatic gluconeogenesis, reduced the peripheral glucose utilization and alter the functions of insulin receptor and post receptor. [29] Corticosteroids increase insulin resistance by directly interfering with glucose transporter type 4 in the muscle cells. [30] [30]

Majority of our patients (57.7%) had a family history of DM. Genetic predisposition and hereditary factors are important risk factors for corticosteroid induced DM.[31] Patients with a family history of DM are at a higher risk of getting DM and the administration of corticosteroids just

increases their risk of developing DM. Therefore, extra precautions should be considered when prescribing corticosteroids to patients at higher risk of developing DM.

Development of corticosteroid induced DM among SLE patients may increase the possibility of cardiovascular comorbidity, such as hypertension. We found that only 19.2% had hypertension. However, the systolic blood pressure in our corticosteroid induced DM cohort was significantly higher than those without DM. This could be confounded by the fact that the corticosteroid induced DM patients were older and increasing age is associated with systolic hypertension. Others have shown that an elevated systolic blood pressure is present in almost all individuals with newly diagnosed diabetes. [32]

We demonstrated elevated complement 3 and 4 in our corticosteroid induced DM patients. The role of complement activation in diabetes has not been fully explored but there is emerging data demonstrating elevated complement 3 with insulin resistance and type 2 DM.[33-35]

In conclusion, corticosteroid induced DM is common in SLE patients receiving corticosteroids with older patients and obese patients at highest risk. Clinicians should be aware and take these factors into consideration when prescribing corticosteroids and screen for the development of corticosteroid induced DM during follow up visits.

Acknowledgement

We would like to thank the Dean of Universiti Kebangsaan Malaysia for giving us a grant to do the above study (FF-2014-050) and for allowing us to publish this data.

REFERENCES

1. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet 2007; 369: 587-96
2. Wang F, Wang CL, Tan CT, Manivasagar M. Systemic lupus erythematosus in Malaysia: a study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. Lupus 1997; 6: 248-53
3. Osio-Salido E, Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. Lupus 2010; 19: 1365-73
4. King JK, Hahn BH. Systemic lupus erythematosus: modern strategies for management: a moving target. Best Pract Res Clin Rheumatol 2007; 21: 971-87
5. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med 2005; 353: 1711-23
6. Hirsch IB, Paauw DS. Diabetes management in special situations. Endocrinol Metab Clin North Am 1997; 26: 631-45
7. Bruce IN. 'Not only. . .but also': Factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatol 2005; 44: 1492–1502
8. Urowitz MB, Gladman DD, Tom BD, Ibanez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol 2008; 35: 2152-8
9. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev 1988; 4: 17-30
10. Chambers SA, Charman SC, Rahman A, Isenberg DA. Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality. Ann Rheum Dis 2007; 66: 1173-7
11. Amal NM, Paramesarvathy R, Tee GH, Gurpreet K, Karuthan C. Prevalence of Chronic Illness and Health Seeking Behaviour in Malaysian Population: Results from the Third National Health Morbidity Survey (NHMS III) 2006. Med J Malaysia 2011; 66: 36-41
12. Ha Y, Lee KH, Jung S, Lee SW, Lee SK, Park YB. Glucocorticoid-induced diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. *Lupus* 2011; 20: 1027-34
13. Kim SY, Yoo CG, Lee CT, Chung HS, Kim YW, Han SK *et al*. Incidence and risk factors of steroid-induced diabetes in patients with respiratory disease. J Korean Med Sci 2011; 26: 264-7
14. Demirci MS, Toz H, Yilmaz F, Ertilav M, Asci G, Ozkahya M,*et al.* Risk factors and consequences of post-transplant diabetes mellitus. Clin Transplant. 2010; 24: 170-7
15. Yates CJ, Fourlanos S, Hjelmesaeth J, Colman PG, Cohney SJ. New-onset diabetes after kidney transplantation-changes and challenges. Am J Transplant. 2012; 12: 820-8
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care 2010; 33: 62-9

17. Yeganeh MZ, Sadeghi S. Risk factors of glucocorticoid-induced diabetes mellitus in systemic lupus erythematosus. GMJ 2013; 2: 39-43
18. Raul Ariza-Andraca C, Barile-Fabris LA, Frati-Munari AC, Baltazar-Montufar P. Risk factors for steroid diabetes in rheumatic patients. Arch Med Res 1998; 29: 259-62
19. Palepu S, Ramesh Prasad GV. New-onset diabetes mellitus after kidney transplantation: Curent status and future directions. World J Diabetes 2015; 6: 445 -55
20. Chiu KC, Lee NP, Cohan P, Chuang LM. Beta cell function declines with age in glucose tolerant Caucasians. Clin Endocrinol 2000; 53: 569–575
21. Rodrigo E, Fernández-Fresnedo G, Valero R, Ruiz JC, Piñera C, Palomar R, *et al*. New-onset diabetes after kidney transplantation: risk factors. J Am Soc Nephrol. 2006; 17: 291–295
22. Davidson J, Wilkinson A, New-onset diabetes after transplantation: 2003 International consensus guidelines. Transplant 2003; 75: 3-24
23. Han E, Kim MS, Kim YS, Kang ES. Risk assessment and management of post-transplant diabetes mellitus. Metabolism 2016; 65: 1559-69
24. Bayés B, Granada ML, Pastor MC, Lauzurica R, Salinas I, Sanmartí A *et al*. Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. *Am J* Transplant. 2007; 7: 416–422
25. Simmons LR, Molyneaux L, Yue DK, Chua EL. Steroid-induced diabetes: is it just unmasking of type 2 diabetes? Endocrinol 2012; 2012:910905.
26. Ito S, Ogishima H, Kondo Y, Sugihara M, Hayashi T, Chino Y, *et al.* Early diagnosis and treatment of steroid-induced diabetes mellitus in patients with rheumatoid arthritis and other connective tissue diseases. Mod Rheumatol 2014; 24: 52-9
27. Kamar N, Mariat C, Delahousse M, Dantal J, Al Najjar A, Cassuto E *et al*. Diabetes mellitus after kidney transplantation: a French multicentre observational study. Nephrol Dial Transplant 2007; 22: 1986-93
28. Hur KY, Kim MS, Kim YS, , Kang ES, Nam JH, Kim SH, *et al.* Risk factors associated with the onset and progression of posttransplantation diabetes in renal allograft recipients. Diabetes care 2007; 30: 609-15
29. Clore JN, Thurby-Hay L. Glucocorticoidinduced hyperglycemia. Endocr Pract. 2009; 15: 469-74
30. Ogawa A, Johnson JH, Ohneda M, McAllister CT, Inman L, Alam T *et al* . Roles of insulin resistance and beta-cell dysfunction in dexamethasone-induced diabetes. J Clin Invest 1992; 90: 497–504
31. Bonato V, Barni R, Cataldo D, Colini A, Ruggieri G, De Bartolomeis C, *et al.* Analysis of posttransplant diabetes mellitus prevalence in a population of kidney transplant recipients. Transplant Proc 2008; 40: 1888-90
32. Czupryniak L, Saryusz-Wolska M , Pawlowski M and Loba J. Elevated systolic blood pressure is present in almost all individuals with newly diagnosed diabetes. J Hum Hypertens 2006; 20: 231–233
33. Wlazlo N**,** Van Greevenbroek MJ, Ferreira I, Feskens EJ, van der Kallen CJ, Schalkwijk CG *et al.* Complement Factor 3 Is Associated With Insulin Resistance and With Incident Type 2 Diabetes Over a 7-Year Follow-up Period: The CODAM Study. Diabetes Care 2014; 37: 1900-1909
34. Muscari A, Antonelli S, Bianchi G, Cavrini G, Dapporto S, Ligabue A, *et al.* Pianoro Study Group. Serum C3 is a stronger inflammatory marker of insulin resistance than C-reactive protein, leukocyte count, and erythrocyte sedimentation rate: comparison study in an elderly population. Diabetes Care 2007; 30: 2362–2368
35. Van Oostrom AJ, Alipour A, Plokker TW, Sniderman AD, Cabezas MC. The metabolic syndrome in relation to complement component 3 and postprandial lipemia in patients from an outpatient lipid clinic and healthy volunteers. Atherosclerosis 2007; 190: 167–173