ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 2, 2016

Online - 2455-3891
Print - 0974-2441

Research Article

CLINICAL AND BIOCHEMICAL PROFILE OF STEROID-INDUCED DIABETES

Karthik Rao N[1]*, Navin Patil[2], Sudha Vidyasagar[1], Rau NR[3], Avinash Manjunath Holla[1], Avinash A[2]

[1]Department of Medicine, Kasturba Medical College, Manipal University, Manipal, Karnataka, India. [2]Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India. [3]Department of Medicine, Yenepoya Medical College, Mangalore, Karnataka, India. Email: vsagar33@yahoo.com

Received: 07 January 2016, Revised and Accepted: 27 January 2016

ABSTRACT

Objective: To study the clinical and biochemical profile of patients who develop steroid-induced diabetes (SID) and its predisposing factors.

Methods: Non-diabetic patients aged ≥18 years started on steroids were considered eligible for the study. In every case after detailed examination, fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycated hemoglobin, fasting insulin were measured prior to starting steroids and was repeated in 1st week (day 3/4) after starting steroid according to standard guidelines. FPG and PPG were repeated periodically during follow-up of the patients. The utility of Indian diabetic risk score (IDRS) score in predicting the risk for SID was also assessed.

Result: Steroid-induced diabetes was found to be more in females than in males. IDRS is not useful in predicting the risk factors of SID. 97% of patients had an elevation of post-prandial sugars with or without fasting hyperglycemia, but only 3% of patients had isolated elevation of fasting blood sugar. 84% of patients developed SID during the 1st week of therapy. 33% of the cases SID persisted even after 1 month of stopping steroids and on a minimal dosage of steroids.

Conclusion: Unlike type 2 diabetes, there were no significant risk factors such as age, family history of diabetes to develop SID and IDRS may not be a sensitive tool for predicting risk factors of SID. Monitoring of post-prandial sugars as compared to fasting sugars is essential for the screening of SID. Cumulative dose of steroid may not be important to precipitate steroid diabetes.

Keywords: Glucocorticoids, Diabetes, Post-prandial glucose, Indian Diabetic Risk Score.

INTRODUCTION

Steroids (synthetic steroids) which are potent anti-inflammatory agents are normally utilized in the treatment of both acute and chronic illness. Their frequent use has resulted in many side effects, which includes osteoporosis and diabetes. The diabetogenic effects of steroids are a limiting factor to their clinical use.

Despite steroid-induced diabetes (SID) being well-known since 1940 [1], the impact of its development and risk factors are poorly quantified. Previous studies suggest that increasing dose, extent of therapy, ethnicity, age, body mass index (BMI), and underlying disease may be risk factors for the development of SID [2-5]. However, the strength of association of risk factors with the development of hyperglycemia remains unclear.

Further, it is not known if SID will remit with discontinuation of steroids. The mechanisms of SID are also not clearly elucidated. Hence, the study was undertaken to study the clinical and biochemical profile of SID.

METHODS

A case-control study was approved by the Institutional Ethics Committee (IEC) of KMC and Hospital, Manipal, Karnataka, India. After obtaining informed consent from non-diabetic patients to be started on steroids admitted in the Medicine, Nephrology, and Neurology wards of Kasturba Hospital, Manipal, Karnataka, India from May 2008 until October 2009 were recruited into the study and followed up until August 2010.

Inclusion criteria

All individuals without diabetes (by American diabetes association (ADA 2007 criteria) [6] to be started on steroids were included in the study. Participants who developed diabetes (according to the ADA criteria for diabetes mellitus, fasting blood sugar >126, and post-prandial blood sugar >200) [6] after having starting steroids and were taken as cases and those who do not develop diabetes were the controls for the study.

Exclusion criteria

All known diabetics, any patient already on steroids, patients on any other drug known to precipitate hyperglycemia and patients in pediatric age group.

Study procedure and data analysis

Based on inclusion-exclusion criteria, a total of 100 patients (n=100) were recruited in the study. Detailed history including family history of diabetes and co-morbidity was recorded. All patients underwent basic anthropometry measurement including height, weight, and waist circumference. The utility of Indian diabetic risk score (IDRS) in predicting the risk for SID was also assessed in the study. Patients who developed hyperglycemia after steroid administration were considered in SID group and those who do not develop hyperglycemia was considered in normoglycemic group.

Fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) were repeated periodically during follow-up of the patients. Appropriate anti-diabetic medication was started, and therapeutic lifestyle modification advised if patients develop diabetes as per their physician's decision. The patients of SID group were followed up for the persistence of diabetes on tapering or after stopping steroids during their follow-up.

Statistical analysis

The analysis was performed using SPSS version 11.0. Data were presented as mean±standard deviation. The normality assumption for continuous variables was evaluated by the Kolmogorov–Smirnov test. The categorical variables were represented as percentages or proportions. Independent sample t-test was done to compare the mean difference between two groups. A $p<0.05$ was considered significant.

RESULTS

A total of 100 eligible patients were included in and their data were analyzed. Out of 100 patients, 59 (59%) were having hyperglycemia after starting steroids, and remaining 41 (41%) patients were normal.

The mean age among cases was 41.76±12.80 and that of controls were 38.76±13.09. This was not statistically significant (p=0.6). The age distribution in number and percentages is shown in Fig. 1, showing that age did not account for a predictive risk factor for SID.

75% (n=44) of steroid-induced diabetics were females as compared to only 25% (n=15) males. This was statistically significant (p=0.008). The percentage of males and females among diabetics and non-diabetics is shown in Figs. 2 and 3.

Among the controls, 48% (n=20) were females as compared with 51% (n=21) males. Among the total of 64 females, 44 (69 %) developed SID, whereas only 15 (41%) out of the total of 36 males developed steroid diabetes. This was again statistically significant (p=0.008) percentage of the total males and females who developed diabetes is shown in Fig. 4.

The mean BMI among cases was 22.26±3.90 and among controls were 22.12±4.28. However, this was not statistically significant (p=0.5). The percentage of patients who developed diabetes under different BMI category is shown in Fig. 5.

The family history of diabetes mellitus was not found to be significant as only 1 patient among cases, and 3 among the controls had positive family history of diabetes mellitus. Similarly, past history of steroid use and presence of hypertension were not found to be significant.

Majority of patients, 66.1% (n=39) cases and 56.1% (n=23) controls had IDRS score between 30 and 60 27.1% (n=6) of the cases and 36.6% (n=15) controls had IDRS score <30. Only 6.8% (n=4) cases and 7.3% (n=3) controls had an IDRS score >60. The IDRS score among the SID and normoglycemic is shown in Fig. 6.

Out of the total of 100 patients, 64 patients were given methyl prednisolone, 35 patients received prednisolone, and 1 received dexamethasone. All the cases received a minimum dosage of 20 mg/day of prednisolone and maximum of 1 g/day of methylprednisolone. The number and percentage of patients who were on various types of steroids are shown in Fig. 7.

In 85% (n=50) of the cases, SID was detected in the 1st week after initiating steroids.10% (n=6) of the cases developed diabetes after 1 week but within 1 month after initiating steroids. Only 5% (n=3) cases developed diabetes 1 month after starting steroids. The detection of SID after the initiation of steroids is shown in Fig. 8.

The detection of SID after the initiation of steroids is shown in Fig. 6. 52% (n=31) of the cases had isolated elevation of post-prandial sugars with normal fasting sugars. 44% (n=26) of the cases had both fasting and post-prandial sugars. Only 3% (n=2) had isolated elevation of fasting sugars with normal post-prandial sugars. The pattern of hyperglycemia among steroid-induced diabetics is shown in Fig. 9.

59.32% (n=35) of the cases were managed by diet control and lifestyle modification 40.67% (n=24) of the cases were started on oral hypoglycemic agents for control of sugars. 6.77% (n=4) of the cases required a combination of insulin and oral hypoglycemic agents. 1.69% (n=1) required control of sugars with insulin alone. The treatment received by the patients is shown in Fig. 10.

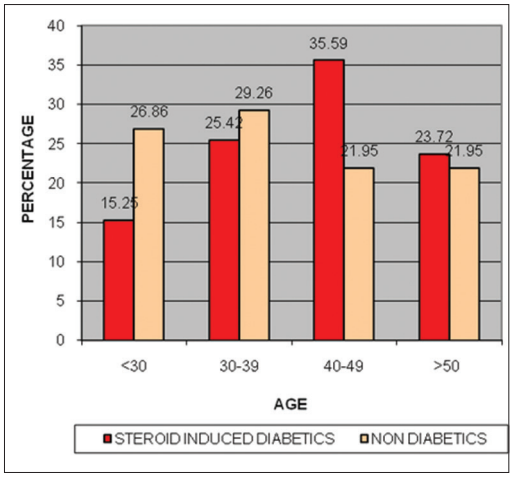

Fig. 1: Age distribution of the population

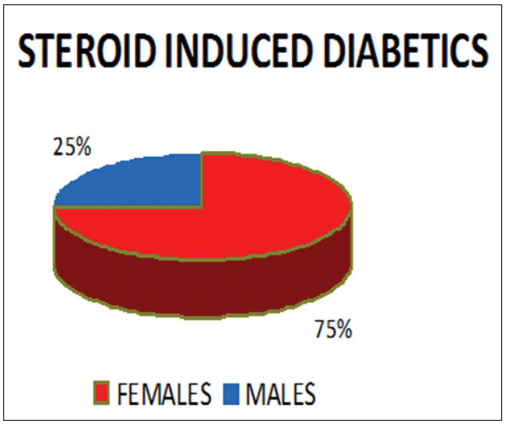

Fig. 2: The percentage of males and females among Diabetics and non-diabetics

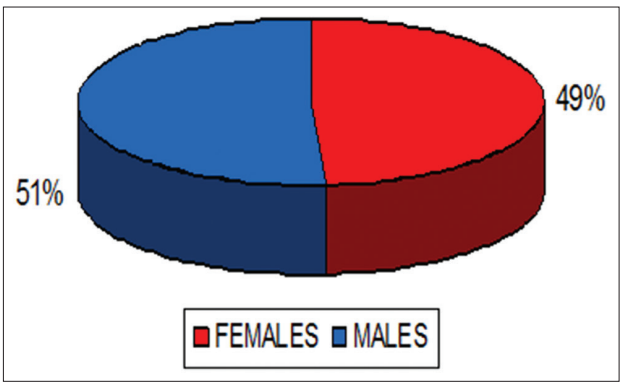

Fig. 3: The percentage of males and females among diabetics and non-diabetics

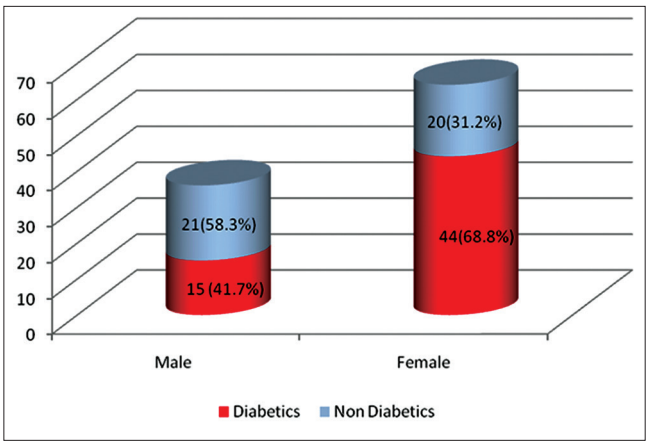

Fig. 4: Percentage of total males and females who developed diabetes

The patients were followed up for a period of 1-year after starting steroids to look for the persistence of diabetes on tapering or after stopping steroids. On tapering doses and after stopping steroids >1 month, it was seen that 66.10% (n=39) cases were in remission. 28.81% (n=17) patients persisted to have SID. The follow-up of patients 1 month after having stopped taking steroids is shown in Fig. 11.

Among them, 23.72% (n=14) cases were on a minimal dosage of steroids (prednisolone 5 mg, methyl prednisolone 4 mg) while 5% (n=3) cases were totally off steroids. 5% (n=3) cases were lost for follow-up.

The difference in pre- and post-fasting insulin levels before and after starting steroids were done among 29 cases and had a mean of 11.72±16.96. Among the 24 controls, the mean was 15.33±16.68. This was not found to be statistically significant. However, the higher insulin reserve among controls than in cases may have prevented them from developing SID probably due to better insulin reserve. These observations merit further studies.

DISCUSSION

The study included 100 patients fulfilling inclusion, exclusion criteria, and found 59 (59%) were having hyperglycemia after starting steroids The incidence of SID was not constant across studies; it ranges from 1.5% to 47%. The variability of this occurrence is due to the differences in patient population, different treatment protocols and definition of diabetes [3].

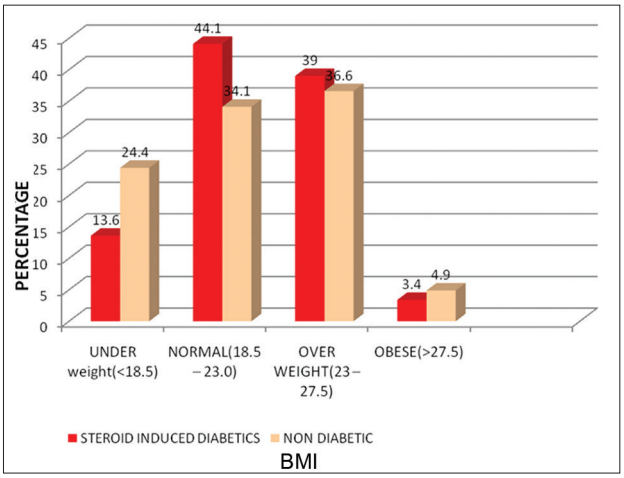

Fig. 5: Percentage of patients who developed diabetes under different categories of body mass index

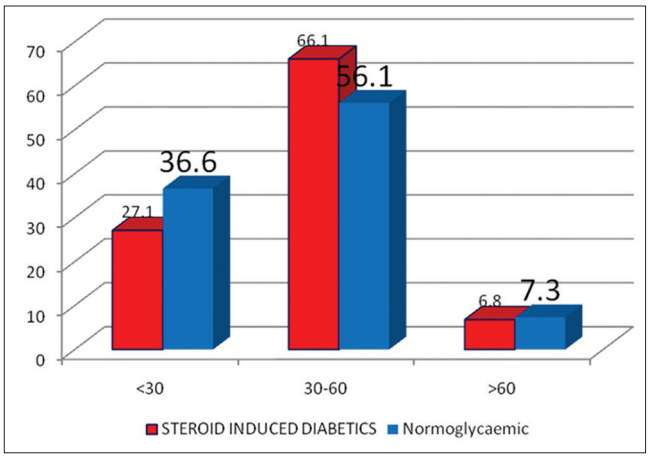

Fig. 6: Indian diabetic risk score among steroid-induced diabetes group and normoglycemia group

In our study, the mean age of persons who developed steroid diabetes was 41 years; the maximum number of patients in our study were in their fourth and fifth decades. We found that 60% (n=40) of the cases were above the age of 40 years, whereas only 40% (n=16) of the controls were in the age group of above 40 years. This was correlating with other studies where the incidence of SID increased with age [7-9]. However, this was not found to be statistically significant (p=0.6). Glucose intolerance may be due to decreased sensitivity of pancreatic cells to glucagon-like peptide 1 and to alterations of hepatic glucose production [10]. These mechanisms may explain the development of SID in the elderly. However, in this study, the risk of developing SID was independent of age.

The study did not show any correlation between family history and the development of steroid diabetes as only one subject among cases and 3 among the controls had positive family history of diabetes mellitus. However, these results may be limited by the fact that the number of patients with family history of diabetes was low. Similarly, past history of steroid use, family history of obesity, and hypertension were not found to be significant.

Similarly, there was no correlation between BMI and development of SID. The mean BMI among cases was 22.26±3.90 and among controls was 22.12±4.28. These findings were consistent with the study by Takuya *et al*. and Raúl Ariza-Andraca *et al*. [9,11]. However, other studies by Arner *et al*. did report a significant correlation with these factors [7].

The risk factors for SID have not been clearly defined. The traditional risk factors for type 2 DM such as age, abdominal obesity, family history, and physical activity have been incorporated in the IDRS [12]. The risk score was derived from the Chennai Urban Rural Epidemiology Study by Mohan *et al*. IDRS depends on the four simple variables, namely age,

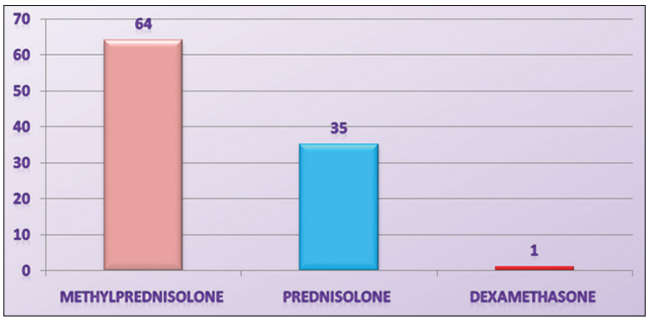

Fig. 7: Number and percentage of patients who were on various steroids

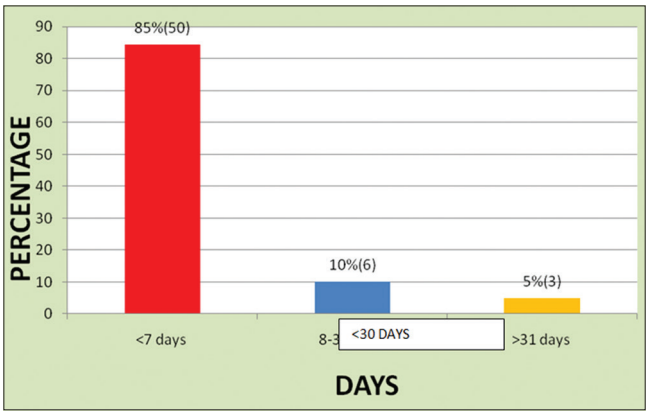

Fig. 8: The time of detection of steroid-induced diabetes after initiation of steroids

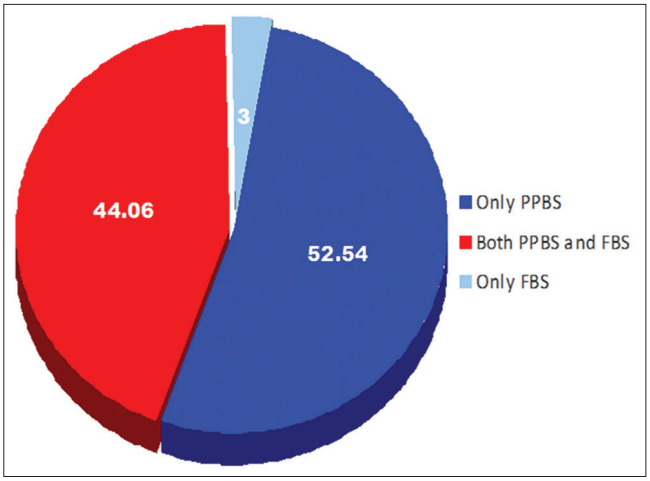

Fig. 9: Pattern of hyperglycemia among steroid induced diabetes

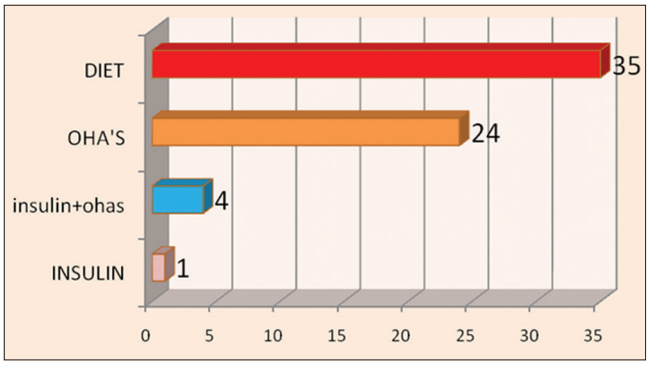

Fig. 10: Treatment received by patients

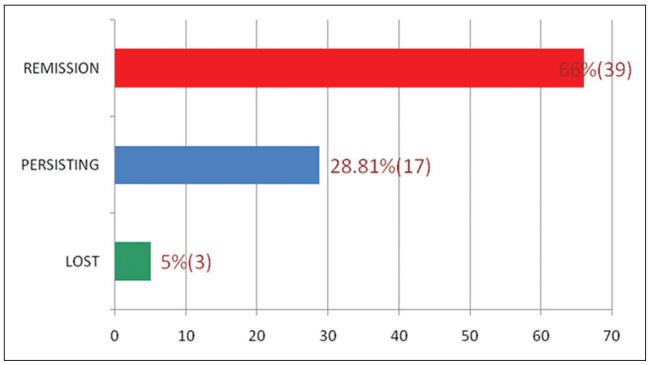

Fig. 11: Follow-up of patients 1 month after stopping steroids

family history of diabetes, waist circumference, and physical activity are used to identify undiagnosed diabetes in the community. Briefly, the definite data on these risk factors was acquired by four questions. These are given scores derived from the logistic regression. Patients with score <30 were divided as low risk, those between 30 and 50 as medium risk and those with ≥60 as high risk for diabetes. IDRS value ≥60 which has sensitivity of 72.5% and specificity 60.1% in detecting undiagnosed diabetes in the general population or its components [12]. Thus, if IDRS can predict the risk of developing SID, further studies can be done to screen the population for undiagnosed diabetes. Follow-up of these individuals who develop type 2 diabetes or have persistence of SID will help us in assessing the utility of IDRS in predicting SID and future risk of type 2 diabetes.

In our study, we analyzed all patients for the presence of these risk factors. We compared the prevalence of these risk factors in cases and controls and found no significant difference in the cumulative scores as well as among the individual risk factors. Consequently, the IDRS score was not useful in predicting the risk of developing SID. Further another study done recently by Vikram *et al*. also showed no correlation between IDRS and SID [13].

In the present study, an attempt was made to quantify the dose of steroid that induced diabetes in susceptible patients. All patients in the study were taking a minimum dose of 30 mg/day or greater of prednisolone while the dose for methylprednisolone was 1 g/day or greater. The literature also shows that hyperglycemia develops in patients who were on a dose of 30 mg/day of prednisolone or its equivalent [14]. Greenstone *et al*. have shown that patients taking alternate day steroid have greater impairment of glucose tolerance on the corticosteroid day than on the alternate day [15].

Further, whether the dose or duration of exposure to steroid causes SID is still controversial across many studies [2,13]. In the present study, 85% of patients developed steroid diabetes within 7 days of starting steroids, whereas a minority had hyperglycemia detected after a month of therapy. This could indirectly imply that cumulative dose may not be a risk factor for steroid diabetes; however, these findings still merit further studies. The fact remains that we must aggressively look for steroid diabetes in the first few weeks after having initiated steroids.

However, there was no statistically significant correlation between the development of steroid diabetes and the cumulative dose of steroid required studies on the cumulative dose show conflicting results across studies [11]. According to Vikram *et al.,* 100% of patients developed SID in the 1st week of steroid exposure [13]. These results indicate that cumulative dose may not be a risk factor [6]. However, other studies by Kim *et al*. and Van Raalte *et al*. [2,4] commented that cumulative dose, and long duration of steroid therapy and susceptibility of the population exposed may be the important risk factors.

The present study found that 97% of patients had an elevation of post-prandial sugars with or without fasting hyperglycemia, but only 3% of patients had isolated elevation of fasting blood sugars. It was previously reported that when only fasting glucose concentration was monitored to detect steroid diabetes, the prevalence of steroid diabetes was 46% in renal transplant recipients who received high dose steroid therapy [7]. Failure to monitor PPG may underestimate the incidence of steroid diabetes cases. Iwamoto *et al*. have reported a close relationship between post-prandial hyperglycemia and SID in patients with neurologic diseases [9]. Their study showed that the mean plasma glucose concentration after lunch was highest among the concentrations at post-prandial points. Although the mean time of maximum plasma concentration and the half-life of prednisolone are 1.3 and 2.2 h after oral administration, respectively [16], the drug might continue to be active during the daytime. Several studies have revealed that post-prandial hyperglycemia including impaired glucose tolerance is a risk factor for mortality [17-19].

In most of the patients, the level of hyperglycemia was around 250 mg/dL. This warranted pharmacotherapy in about 50% of the patients, most of them being on oral hypoglycemic agents. The rest were being managed with lifestyle modifications; however, a previous study had reported that steroid diabetes is similar to type 2 diabetes mellitus, except that it often requires insulin therapy [7]. The literature states that if the FPG is near normal range, oral diabetic agents (e.g. sulfonylureas, metformin) maybe sufficient to reduce hyperglycemia. However, if the FPG is >200 mg/dl, oral agents are usually not efficacious, and insulin therapy is required. Trence *et al*. have reported that steroid diabetes is treated primarily with prandial insulin, either regular or rapid insulins (lispro or aspart), intermediate insulin being indicated less frequently for fasting hyperglycemia [20].

In a preliminary follow-up of patients who had stopped steroids for more than 1 month or were on the tapering dosage of steroids, it was found

that about 33% persisted to have sugars in the diabetes range. Thus, steroids may be unmasking diabetes in a significant number of patients which will have to be confirmed by future studies. There are conflicting results on the persistence of hyperglycemia on stopping steroids. Some studies reported that impaired glucose tolerance-induced by steroids may continue for about 24 h when the steroid is administered once a day [21]. Vikram *et al*. have reported that sugars come to the normal range 1 week after stopping therapy while some have also reported that the effect of glucocorticoids on hyperglycemia usually remit within 48 h of discontinuation of oral administration [13,22].

Diabetic ketoacidosis is a rare complication of steroid-induced diabetes [23]. In our study, no patient developed diabetic ketoacidosis or other acute complications of hyperglycemia.

CONCLUSION

To conclude, the study did not reveal any significant risk factors which could predict the development of SID. The IDRS, which was very useful in predicting the risk of type 2 diabetes, was not found helpful in determining the risk of developing SID.

Steroid-induced diabetes is essentially an exaggeration of post-prandial hyperglycemia. Hence, monitoring of post-prandial sugars as compared to fasting sugars is essential, especially in the 1st week after initiating steroids. The majority of individuals who develop SID can be managed with diet and lifestyle modification without any pharmacological therapy.

In almost 30% of the cases, SID persisted even after 1 month of stopping steroids when on a minimal dosage of steroids. Thus, there is a significant reason to believe that steroids may aid in the unmasking of diabetes in a significant number of patients. Further, studies are to be undertaken to validate this hypothesis.

REFERENCES

1. Ingle DJ. The production of glycosuria in the normal rat by means of 17-hydroxy dehydroxycorticosterone. Endocrinology 1941;29:649-57.
2. 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(2):264-7.
3. Simmons LR, Molyneaux L, Yue DK, Chua EL. Steroid-induced diabetes: Is it just unmasking of Type 2 diabetes? ISRN Endocrinol 2012;2012:910905.
4. van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: Towards expansion of therapeutic options? Eur J Clin Invest 2009;39(2):81-93.
5. Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, *et al.* Glucocorticoid-induced diabetes mellitus: Prevalence and risk factors in primary renal diseases. Nephron Clin Pract 2007;105(2):c54-7.
6. American Diabetes Association. Diabetes care. J Clin Appl Res Educ 2015;38:S1-93.
7. Arner P, Gunnarsson R, Blomdahl S, Groth CG. Some characteristics of steroid diabetes: A study in renal-transplant recipients receiving high-dose corticosteroid therapy. Diabetes Care 1983;6(1):23-5.
8. Aisen PS, Berg JD, Craft S, Peskind ER, Sano M, Teri L, *et al.* Steroid-induced elevation of glucose in Alzheimer's disease: Relationship to gender, apolipoprotein E genotype and cognition. Psychoneuroendocrinology 2003;28(1):113-20.
9. Iwamoto T, Kagawa Y, Naito Y, Kuzuhara S, Kojima M. Steroid-induced diabetes mellitus and related risk factors in patients with neurologic diseases. Pharmacotherapy 2004;24(4):508-14.
10. Elahi D, Muller DC, Egan JM, Andres R, Veldhuist J, Meneilly GS. Glucose tolerance, glucose utilization and insulin secretion in ageing. Novartis Found Symp 2002;242:222-42.
11. Raúl Ariza-Andraca C, Barile-Fabris LA, Frati-Munari AC, Baltazár-Montufar P. Risk factors for steroid diabetes in rheumatic patients. Arch Med Res 1998;29(3):259-62.
12. Mohan V. A simplified Indian diabetes risk score for screening for undiagnosed diabetic subjects. J Assoc Physicians India 2005;53:759-63**.**
13. Shanbhogue VV, Vidyasagar S, Madken M, Varma M, Prashant CK, Seth P, *et al.* Indian diabetic risk score and its utility in steroid induced diabetes. J Assoc Physicians India 2010;58:202.
14. Lieberman P, Patterson R, Kunske R. Complications of long-term steroid therapy for asthma. J Allergy Clin Immunol 1972;49(6):329-36.
15. Greenstone MA, Shaw AB. Alternate day corticosteroid causes alternate day hyperglycaemia. Postgrad Med J 1987;63(743):761-4.
16. Schummer BP, Parker KL. Adrenacortical steroids and their synthetic analogs. In: Hardman JG, Limbird LE, Gilman AG, editors. Goodman and Gilman's Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill; 2001. p. 1655-75.
17. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M. Post-challenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. Diabetes Care 2000;23(12):1830-4.
18. Barrett-Connor E, Ferrara A. Isolated post-challenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men. The Rancho Bernardo Study. Diabetes Care 1998;21(8):1236-9.
19. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care 1999;22(6):920-4.
20. Trence DL. Management of patients on chronic glucocorticoid therapy: An endocrine perspective. Prim Care 2003;30(3):593-605.
21. Henriksen JE, Alford F, Ward GM, Beck-Nielsen H. Risk and mechanism of dexamethasone-induced deterioration of glucose tolerance in non-diabetic first-degree relatives of NIDDM patients. Diabetologia 1997;40(12):1439-48.
22. Hoogwerf B, Danese RD. Drug selection and the management of corticosteroid-related diabetes mellitus. Rheum Dis Clin North Am 1999;25(3):489-505.
23. Agarwal PK, Jeloka T, Sharma AP. Steroid-induced diabetes mellitus presenting as diabetic ketoacidosis. Indian J Nephrol 2002;12:122-3.