International Journal of Research in Medical Sciences
Suresh RM et al. Int J Res Med Sci. 2023 May;11(5):1709-1713
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20231341

Original Research Article

Incidence of steroid-induced diabetes mellitus among in-patients treated for COVID-19 infection in tertiary care centre

Suresh R. M., Abhishek T. M., Girish P., Anjali V.*, Venugopal K.

Department of General Medicine, Hassan Institute of Medical Sciences, Hassan, Karnataka, India

Received: 14 March 2023
Accepted: 13 April 2023

***Correspondence:**
Dr. Anjali V.,
E-mail: abhishek.atm4@gmail.com

ABSTRACT

Background: Glucocorticoids are one of the most effective lifesaving treatments for severe COVID-19 infection. The aim of this study was to review the incidence of glucocorticoid-induced diabetes and its associated risk factors in COVID-19 patients.
Methods: This was a retrospective cohort study, Hassan institute of medical sciences, Hassan, Karnataka, from 1st July 2020 to 31st December 2021. Data were collected from the medical record department of all RTPCR/RAT-positive cases of COVID-19 patients admitted and treated for COVID-19, with a sample size of 521 patients.
Results: In the present study of 521 patients with COVID-19 who received glucocorticoid therapy, 72 (13.8%) of the patients experienced GI-DM. In our series of 521 patients treated with steroid for respiratory diseases, old age and chronic smoking was an independent risk factor for GI-DM. Glucose tolerance declines progressively with age, resulting in a high incidence of type 2 diabetes and impaired glucose tolerance in the old population.
Conclusions: In conclusion, this study found that 13.8% of in-patients treated for COVID-19 infection in a tertiary care centre developed GI-DM. The incidence of GI-DM was higher among patients who were older, had a history of smoking, and had hyperlipidaemia or malignancy. The study highlights the importance of monitoring blood glucose levels in patients receiving steroids for the treatment of COVID-19. Additionally, the results suggest that patients with certain risk factors may benefit from closer monitoring of blood glucose levels.

Keywords: COVID-19, Diabetes mellitus, Glucocorticoids, Glucocorticoid-induced diabetes mellitus, Hyperglycaemia, SARS-CoV-2, Steroids.

INTRODUCTION

Since glucocorticoids emerged at the surface of medicine in the last century (the 1950s), glucocorticoids have been a central role in managing different inflammatory diseases by decreasing inflammation and minimizing tissue damage.[1] This includes respiratory diseases but is not limited to, chronic obstructive pulmonary disease (COPD), interstitial and hypersensitivity pneumonitis, sarcoidosis, endo-bronchial and extra-pulmonary tuberculosis. This anti-inflammatory benefit of steroids comes with some price in the form of various adverse effects like fluid accumulation leading to oedema, increased blood pressure, menstrual disturbance, weight gain, Cushing's syndrome, gastric ulceration, insomnia, psychosis and recurrent infections due to suppression of immunity. Impaired metabolism of glucose is the most common untoward effect encountered. Glucocorticoids not only increase the episodes of high blood glucose levels in already known diabetic patients but can also cause elevated blood glucose levels leading to diabetes in patients with no prior history of diabetes mellites.[2] Mostly, this condition of raising

blood sugar levels is temporary, but some cases may develop clinical manifestations of diabetes like persistent polydipsia, polyuria, and repeated infections where the treatment with glucocorticoids merely seem to uncover hidden diabetes. When starting a patient on steroids, especially in geriatric patients, there is a chance of causing a non-ketotic hyperosmolar state and hyperglycaemic state which may progress to coma.

If persistent, increase in blood glucose can increase the risks of developing cardiovascular disease and microvascular complications. We reviewed the incidence and associated risk factors leading to steroid-induced diabetes mellitus (GI-DM) in COVID-19 patients with respiratory complications.[3-5] Hyperglycaemia is common in critical illness, associated with increased mortality and is potentially dangerous in all critically ill patients, including those with COVID-19 infection.[6] Hyperglycaemia appears to be an independent risk factor for admission to the intensive care unit (ICU) in COVID-19 patients. Worldwide, limited attention has been given to the potential adverse effects of steroid therapy. Awareness of the risk of impaired glycaemic control is much needed in the current situation where we are expecting the fourth wave of COVID-19.[7]

Previous studies shows that 53-70% of individuals without diabetes develop steroid-induced hyperglycaemia.[8] An Australian study of 80 hospitalized people without diabetes reported that 70% of subjects had at least one blood glucose measurement of >180mg/dl (≥10 mmol/L).[9] A meta-analysis of 13 studies showed that overall, 32.3% of people developed glucocorticoid-induced hyperglycaemia and 18.6% developed frank diabetes.[10] Use of steroids, particularly following the publication of the recovery trial with the use of dexamethasone in people admitted to the hospital with COVID-19, may therefore also be associated with an increased risk of developing diabetes, which again could be directly related to steroid-induced abnormalities with the delayed or blunted recovery of βcell damage. [11]

Objectives of the study were to determine the incidence of steroid-induced DM among in-patients treated for covid-19 infection, to determine the risk factors associated with steroid-induced hyperglycaemia and frank diabetes in COVID-19 infection.

METHODS

Data were collected from the medical record department of all RTPCR/RAT-positive cases of COVID-19 patients admitted and treated for COVID-19 in the dedicated COVID hospital (DCH) Hassan, from 1st June 2020 to 31st December 2021. A retrospective cohort study was conducted, with a sample size of 521 patients. As per the inclusion criteria, all COVID positive patients, admitted to ICU and COVID wards with moderate to severe COVID-19 infection who had received steroids as part of the standard treatment protocol as per the ICMR guidelines, while exclusion criteria excluded pre-existing diabetes, random sugar levels greater than 200mg/dl at the time of admission, patients already taking steroids for other medical conditions, and patients who had received steroids less than 21 days.

Patient data, demographics, and laboratory findings were collected and the frequency of occurrence of hyperglycaemia was documented during the 21-days period. As per ADA criteria, patients with FBS 126mg/dl or higher, and RBS 200mg/dl or higher were considered 'with GI-DM,' while the rest of the patients were classified as 'without GI-DM.'

Student's 't' -test was used to compare and analyse continuous variables between two groups of patients (with and without GI-DM) while the Chi-square test was applied to the categorical variables. Multiple logistic regression models were used to find out the predicting factors for GI-DM. Statistical significance was considered if $p < 0.05$, and all statistical analyses were performed using SPSS-20.

RESULTS

The study investigated the incidence of steroid-induced diabetes among in-patients treated for COVID-19 infection in a tertiary care centre. A total of 521 patients were included in the study, with 72 patients (13.8%) developing GI-DM and 449 patients (86.2%) without GI-DM. Among 521 patients 314 (60.2%) were females and 207 (39.8%) were males. And there was no significant difference in the incidence of steroid-induced diabetes among males (52.9%) and females (47.1%, with p=0.096).

The patients with GI-DM had a significantly higher mean age (65 years) compared to patients without GI-DM (53 years) (p=0.001), this observation implies that elderly patients were at higher risk of developing GI-DM. However, there was no significant difference in body mass index (BMI) between the two groups (p=0.563).

Patients with GI-DM had a significant correlation with chronic smoking with higher pack-year history (23.1) compared to patients without GI-DM (8.5) (p=0.003). There was no significant difference in the mean values of random glucose, creatinine, or cholesterol levels between the two groups during the period of three weeks (p=0.625, 0.596, and 0.625, respectively). Patients with GI-DM had a significantly longer total duration of hospital stay (36 days) compared to patients without GI-DM (23 days) (p=0.001).

The study also compared the characteristics of patients with and without GI-DM. The results showed that current or ex-smokers (55.9%) were at higher risk of developing GI-DM compared to non-smokers (31%, p=0.005). Additionally, patients with chronic kidney disease (3%) were less likely to develop GI-DM compared to patients without chronic kidney disease (5.1%, p=0.001).

Table 1: Incidence of GI-DM among in-patients treated for covid-19 infection

Characteristics	All patients (n-521)		Patients with GI-DM (n=72)		Patients without GI-DM (n=449)		
Number of subjects	N	%	N	%	N	%	**P value**
Male sex (%)	207	40	38	53	169	38	0.096
Female sex (%)	314	60	34	47	280	62	

Table 2: Risk factors associated with GI-DM

Characteristics	All patients (n-521)		Patients with GI-DM (n=72)		Patients without GI- DM (n=449)		P value
	Mean	SD	**Mean**	SD	**Mean**	SD	
Age, (years)	55	13	65	9	53	13	0.001
Body mass index (kg/m^{2})	23.2	3.7	23.6	3.2	22.9	3.8	0.563
Somking Pack-years	10.7	20.2	23.1	25.5	8.5	18.4	0.003
Random glucose (mg/dL)	101	13	123	21	101	14.1	0.625
Creatinine (mg/dL)	0.9	0.3	1.9	0.4	0.9	0.3	0.596
Cholesterol (mg/dL)	179	14	186	17	178	19	0.625
The total duration of Hospital Stay	28	7	36	13	23	9	0.001

Table 3: Associated risk factors in COVID-19 infection for GI-DM.

Characteristics	All patients (n-521)		Patients with Steroid induce DM (n=72)		Patients without steroid-induced DM (n=449)		
Current or ex-smoker	180	34.6	40	55.9	139	31	0.005
Hypersensitive pneumonitis	7	1.3	0	0	7	1.5	n/a
Hypertension	80	15.4	18	25	62	13.8	0.362
Hyperlipidaemia	28	5.3	9	12.5	18	4.1	0.065
Chronic kidney disease	25	4.8	2	3	23	5.1	0.001
Chronic liver disease	7	1.3	0	0	7	1.5	n/a
Malignancy	23	4.4	5	6.5	18	4.1	0.001

Table 3: Associated risk factors in COVID-19 infection for GI-DM.

Parameters	Odds ratio	95% confidence interval	P value
Age (years)	1.15	(1.02-1.09)	0.001
Gender	1.6	(0.48-5.99)	0.469
Smoking	1.23	(0.29-6.32)	0.658
Pack-years	1.09	(0.99-1.05)	0.256
Hyperlipidaemia	2.14	(0.47-9.47)	0.362
Idiopathic interstitial pneumonias	1.21	(0.36-3.86)	0.254
Endobronchial tuberculosis	0.59	(0.06-2.31)	0.681

Similarly, there was no significant difference in the incidence of GI-DM among patients with hypertension (25%) and without hypertension (13.8%, p=0.362). However, patients with dyslipidaemia (12.5%, p=0.065) and malignancy (6.5%, p=0.001) were more likely to develop GI-DM compared to patients without these conditions.

The study found that GI-DM was relatively common among in-patients treated for COVID-19 infection in a tertiary care centre, with smokers, patients with hyperlipidemia, and malignancy being at higher risk for developing GI-DM. The study highlights the importance of monitoring blood glucose levels in patients receiving steroids for the treatment of COVID-19.

The odds ratio for age was 1.15, with a 95% confidence interval of (1.02-1.09), and a p value of 0.001. This suggests that there was a significant association between age and steroid induced DM for gender, the odds ratio was

1.6, with a 95% confidence interval of (0.48-5.99), and a p value of 0.469. This suggests that there was no significant association between gender and steroid induced DM. For smoking, the odds ratio was 1.23, with a 95% confidence interval of (0.29-6.32), and a p value of 0.658. This suggests that there was no significant association exists between smoking and steroid induced dm. The possible explanation for these values was a significant number of patients were females (317) and they are non-smokers. Only male patients with a history of smoking were considered.

for pack years, the odds ratio was 1.09, with a 95% confidence interval of (0.99-1.05), and a p value of 0.256. This suggests that there was no significant association exists between pack-years and steroid induced dm. The possible explanation for these values was a significant number of patients were females (317) and they are non-smokers. Only male patients with history of smoking were considered. For dyslipidaemia, the odds ratio was 2.14, with a 95% confidence interval of (0.47-9.47), and a p value of 0.362. This suggests that there was no significant association exists between dyslipidaemia and steroid induced dm.

for idiopathic interstitial pneumonias, the odds ratio was 1.21, with a 95% confidence interval of (0.36-3.86), and a p value of 0.254. This suggests that there was no significant association between idiopathic interstitial pneumonias and steroid induced DM. For endobronchial tuberculosis, the odds ratio was 0.59, with a 95% confidence interval of (0.06-2.31), and a p value of 0.681. This suggests that there was no significant association between endobronchial tuberculosis and steroid induced DM.

DISCUSSION

Glucocorticoids can cause hyperglycaemia via insulin resistance, which augments hepatic gluconeogenesis and lowers glucose uptake by peripheral tissues such as muscle cells and adipocytes.[12,13] For these reasons, it is not uncommon to observe abnormal glucose tolerance among patients receiving steroid therapy. In the present study of 521 patients with COVID-19 who received glucocorticoid, 72 (13.8%) of the patients experienced GI-DM. Given that the incidence of GI-DM in other conditions requiring glucocorticoids, such as connective tissue diseases, was between 0.4% and 5.4%,[14-18] the proportion of patients with COVID-19 treated with steroid who developed GI-DM in our study is comparable. The wide variability may reflect different study populations, doses of glucocorticoid, duration of follow-up, and different diagnostic criteria for GI-DM.

Proposed risk factors for GI-DM included old age, high BMI, impaired glucose tolerance before therapy, cumulative dose, and long duration of steroid therapy. However, these results were not always consistent across studies.[17-20] In our series of 521 patients treated with steroid for respiratory diseases, old age and chronic smoking was an independent risk factor for GI-DM. Glucose tolerance declines progressively with age, resulting in a high incidence of type 2 diabetes and impaired glucose tolerance in the old population.[21,22] According to the Korean National Health and Nutrition Examination Survey, 45% of subjects, 65 years and older meet the diagnostic criteria for type 2 diabetes or impaired glucose tolerance.[23] With aging, beta-cell function declines, and basal insulin secretion level decreases.[24] In addition, the interaction of many factors associated with aging likely contributes to the altered glucose tolerance. These factors include obesity, decreased physical activity, medications, and coexisting illness.[25] Considering the vulnerability of the aged population to glucose intolerance, the association of GI-DM and age in our study can be understood. Going by this observation there is a possibility that COVID-19 infection directly affects beta cell function which was further compounded by the prolonged administration of steroids thereby causing frank type 2 diabetes millets.

CONCLUSION

In conclusion, this study found that 13.8% of in-patients treated for COVID-19 infection in a tertiary care centre developed GI-DM. The incidence of GI-DM was higher among patients who were older, had a history of smoking, and had hyperlipidemia or malignancy. The study highlights the importance of monitoring blood glucose levels in patients receiving steroids for the treatment of COVID-19. Additionally, the results suggest that patients with certain risk factors may benefit from closer monitoring of blood glucose levels. Overall, this study provides important information for clinicians treating COVID-19 patients with steroids and suggests that individualized treatment plans may be necessary for patients at higher risk of GI-DM.

Recommendations

Follow-up of these GI-DM patients for at least six months could have given more information about their blood sugar status and mode of treatment with respect to the need to continue insulin therapy & the use of oral hypoglycaemic agents. Since the study was a retrospective cohort study, follow-up of these patients was not taken up.

ACKNOWLEDGEMENTS

Authors would like to acknowledge their medical superintendent Dr Krishnamurthy VR for his timely permission to access the medical records, also to all General Medicine department colleagues for their active input throughout the study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. De Bosscher K, Vanden Berghe W, Haegeman G. Mechanisms of anti-inflammatory action and of immunosuppression by glucocorticoids: negative interference of activated glucocorticoid receptor with transcription factors. J Neuroimmunology. 2000;109:16-22.
2. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15:469-74.
3. Swafe L, Narwani V, Stavraka C, Dhatariya K. How frequently are bedside glucose levels measured in hospital inpatients on glucocorticoids Clin Med. 2014;14:327-28.
4. Nathan DM, Genuth S, Lachin J, Cleary P. The diabetes control and complications trial research group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-86.
5. Tryfon S, Papanas N. Corticosteroid-induced diabetes in patients with chronic obstructive pulmonary disease. Clin Pulm Med. 2008;15:127-31.
6. Stoudt K, Chawla S. Don't sugar coat it: glycemic control in the intensive care unit. J Intensive Care Med. 2019;34:889- 96.
7. Perez HE, Flores DL, Gutierrez R, Gonzalez JG, Tamez-Pena AL. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. World J Diabetes. 2015;6:1073-81.
8. Cheung NW. Steroid-induced hyperglycaemia in hospitalised patients: does it matter. 2016;59:2507-09.
9. Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. Ann Nutr Metab. 2014;65:324-32.
10. Bornstein SR, Rubino F, Khunti K. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020;8:546-50.
11. Accili D. Can COVID-19 cause diabetes? Nature Metabolism. 2021;4:1-3.
12. Clore JN, Thurby L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15:469-74.
13. Tryfon S, Papanas N. Corticosteroid-induced diabetes in patients with chronic obstructive pulmonary disease. Clin Pulm Med. 2008;15:127-31.
14. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Posttransplantation diabetes: a systematic review of the literature. Diabetes Care. 2002;25:583-92.
15. Panthakalam S, Bhatnagar D, Klimiuk P. The prevalence and management of hyperglycaemia in patients with rheumatoid arthritis on corticosteroid therapy. Scott Med J. 2004;49:139-41.
16. Smyllie HC, Connolly CK. Incidence of serious complications of corticosteroid therapy in respiratory disease. A retrospective survey of patients in the Brompton hospital. Thorax. 1968;23:571-81.
17. 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;105:54-7.
18. 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;24:508-14.
19. Andraca C, Fabris LA, Munari AC, Montufar P. Risk factors for steroid diabetes in rheumatic patients. Arch Med Res. 1998;29:259-62.
20. 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;6:23-5.
21. Iozzo P, Nielsen H, Laakso M, Smith U, Järvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. J Clin Endocrinol Metab. 1999;84:863-8.
22. Kim SG, Yang SW, Choi SI, Park SH, Lee KR, Park JH, et al. Prevalence of diabetes mellitus in the elderly of Namwon county, South Korea. Korean J Med. 2001;60:555-66.
23. Korean National Health and Nutrition Examination Survey. 2008. Available at http://knhanes.cdc.go.kr. Accessed on 13 January 2023.
24. Thearle M, Brillantes AM. Unique characteristics of the geriatric diabetic population and the role for therapeutic strategies that enhance glucagon-like peptide-1 activity. Curr Opin Clin Nutr Metab Care. 2005;8:9-16.
25. Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab. 2003;284:7-12.

Cite this article as: Suresh RM, Abhishek TM, Girish P, Anjali V, Venugopal K. Incidence of steroid-induced diabetes mellitus among in-patients treated for COVID-19 infection in tertiary care centre. Int J Res Med Sci 2023;11:1709-13.