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RISK FACTORS AND INCIDENCE OF STEROID INDUCED HYPERGLYCEMIA

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ABSTRACT

Steroid induced hyperglycaemia is a well established but often under-reported side effect of glucocorticoid therapy. Hyperglycemia leads to poorer hospital outcomes and increases mortality. Identification of risk factors of hyperglycemia leads to early detection and treatment of this complication. A total of 112 patients admitted or attending Nizams Institute of Medical Sciences were enrolled after meeting the inclusion and exclusion criteria. History, demographic data and other baseline investigations were recorded. Patients who developed hyperglycemia as a complication were designated as cases and those who did not as controls. Risk factors were compared between the two groups and Hazard ratio calculated. Time to development of hyperglycemia was also assessed. The incidence of steroid induced hyperglycemia was 37.5% in this study. Females had a higher incidence of developing the event than males. A higher BMI, family history of DM, female sex and a sedentary lifestyle were found to be associated with an increased risk of developing hyperglycaemia in this study. Hyperglycemia was more common in the first week of starting steroids. Postprandial hyperglycemia was more common than fasting hyperglycaemia.

KEYWORDS: Hyperglycemia, Risk Factors, Incidence

Steroids are widely prescribed for their anti-inflammatory and immunosuppressive properties but steroids have several side effects like osteoporosis, dyslipidemia, central obesity, adrenal suppression etc. (Ha *et al.*, 2011) (van Raalte *et al.*, 2009)

Hyperglycaemia is the most representative and common. Glucocorticoids are the most common cause of drug induced diabetes (Lansang and Hustak, 2011). Steroids not only exacerbate hyperglycaemia in patients with known diabetes mellitus but also cause DM in patients without documented hyperglycaemia before the initiation of glucocorticoid therapy. (Trence, 2003) (Hirsch and Paauw, 1997)

The effects of steroids on glucose homeostasis are due to multiple mechanisms like reduced peripheral insulin sensitivity, increase in glucose production through promotion of hepatic gluconeogenesis, beta-cell injury, impaired insulin release, inhibited glyceroneogenesis and increase in fatty acids. (van Raalte *et al.*, 2009) (Hwang and Weiss, 2014) (Geer et al., 2014)

A higher dose of glucocorticoid, longer duration of treatment, advanced age, high body mass index, personal history of gestational diabetes, previous glucocorticoid induced hyperglycaemia, family history of diabetes mellitus and a HbA1c >/= 6% have been identified as risk factors by studies (Fathallah *et al.*, 2015) (Perez *et al.*, 2014) (Mills and Devendra, 2015). Steroids affect post prandial blood glucose levels more than fasting levels (Lansang and Hustak, 2011) (Roberts *et al.*, 2018). Steroid induced diabetes can start at any point after commencing treatment but is more likely in the first week of treatment with high dose steroids. High dose steroids can be associated with significant hyperglycaemia, including development of hyperglycaemic hyperosmolar syndrome and even diabetic ketoacidosis in patients with type 1 DM. (Mills and Devendra, 2015)

Hyperglycaemia leads to longer hospital stays, increased risk of infections and delayed wound healing (Roberts *et al.*, 2018). Identification of impaired glucose tolerance during steroid treatment can lead to a shift to steroid sparing therapy or optimising treatment with insulin or oral hypoglycaemic agents.

Although steroid induced hyperglycaemia is an established adverse effect, the reason as to why only few patients develop this event needs to be explored. Therefore, this study aims to estimate the incidence and identify the risk factors associated with the development of steroid induced hyperglycaemia.

METHODOLOGY

A prospective observational study was done over one year from August 2019 to August 2020 by the department of General Medicine in Nizam's Institute of Medical Sciences, a tertiary care hospital in Hyderabad, Telangana.

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Inclusion Criteria

All subjects who were started on systemic steroids (IV/Oral) with a dose more than or equal to prednisone 5mg for any indication, patients aged more than 18 and less than 60 years and those who gave written informed consent were included in our study.

Exclusion Criteria

Participants who were diagnosed as type 1 or type 2 Diabetes Mellitus, participants using inhalational or topical steroids, those with a history of using systemic steroids (IV/Oral) in the past 3 months and a baseline blood glucose of > 200mg/dl were excluded from our study. Pregnant and lactating women, subjects with hepatic and renal impairment were also excluded.

Subjects admitted or attending Nizam's Institute of Medical Sciences, requiring steroids for indications like immune thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis, etc. were recruited. Detailed history, demographic details, BMI, family history of diabetes, history of gestational diabetes, underlying condition and indication for starting steroids and the dosage regimen along with duration was recorded for all patients enrolled in the study. Investigations like complete blood picture, renal function tests and liver function tests, and HbA1c were recorded. Baseline blood glucose was recorded before starting steroids in all subjects. Patients who did not develop hyperglycaemia were followed up for a maximum duration of 1 month.

Fasting, post prandial and pre-evening meal glucose measurements were recorded thrice daily for in-patients for entire duration of hospital stay and fasting and post prandial blood sugars were recorded for out-patients once a week during follow up, for 1 month. Subjects who developed steroid induced hyperglycaemia within one month were taken as cases and those who did not develop hyperglycaemia within one month were taken as controls for the analysis of risk factors. Risk factors that were assessed were body mass index, age, history of gestational diabetes mellitus, family history of diabetes, dose and duration of steroids.

Statistical Analysis

The primary outcome was to calculate the Hazard ratio associated with the risk factors and the secondary outcomes were to find out the proportion of patients who develop steroid induced hyperglycaemia, to assess the time to development of hyperglycaemia and to find out the difference in mean dose of steroids between cases and controls. A sample size of 112 patients was estimated, to enroll 40 cases considering 6.35 as odds ratio for development of event and 50% prevalence of steroid induced hyperglycaemia with 5% level of significance, 80% power, 20% screen failure and 20% drop out rates.

RESULTS

All the patients were categorised into underweight (<18.5 kg/m2), normal (18.5-22.9kg/m2), overweight (23-27.5kg/m2) and obese (>27.5 kg/m2) based on BMI. Among the cases, 54.8% were overweight and 28.6% were obese, while in controls 51.4% were overweight and none were obese (p- 0.001). Among the patients who were obese, one patient developed DKA after a single dose of glucocorticoid therapy.

The dose of corticosteroid administered was converted into an equivalent dose of prednisolone (George). The median equivalent dose of prednisolone in cases was 200 mg and among controls was 100 mg (p value -0.001).

Table 1: Comparison of demographic data of cases and controls

	Hyperglycaemic Event	N	Mean	Std. Deviation	p Value
Age (yrs)	YES	42	37.857	10.1994	0.635
	NO	70	38.957	12.7216	
Height (cms)	YES	42	163.762	6.8532	0.029
	NO	70	167.094	8.1679	
Weight (kgs)	YES	42	69.000	10.5784	0.003
	NO	70	62.757	10.7871	
BMI (kg/m2)	YES	42	25.7688	3.57161	0.001
	NO	70	22.3877	3.05891	
HbA1C	YES	42	5.579	.6513	0.542
	NO	70	5.649	0.5453	
GRBS	YES	42	89.95	8.18	0.34
	NO	70	88.35	8.73	

BMI- Body mass index, HbA1C- glycosylated haemoglobin. GRBS- General random blood sugar, p value < 0.05 considered statistically significant

61.9% of cases had a family history of DM in a first degree relative as compared to only 25.7% in the controls (p value- 0.001). Of the females who developed hyperglycaemia 9 of them had a history of GDM as compared to only 4 in controls. (p- 0.150). Patients were categorised into three groups based on whether they had an active lifestyle, lifestyle with moderate activity or a sedentary lifestyle taking into account both exercise and non- exercise physical activity (Tamez Perez *et al.*, 2012) (Tokyo: Ministry of Health, Labour and Welfare of Japan; 2006). 47 patients in the control group had an active lifestyle as compared to 19 patients in the hyperglycaemic group (p value <0.05).

AIHA- Autoimmune hemolytic anemia, AOSD- Adult onset still's disease, APLA- Anti- phospholipid antibody syndrome, COVID- Corona virus disease, ITP- Immune thrombocytopenic purpura, GN- Glomerulonephritis, RA- Rhematoid arthritis, SLE- Systemic lupus erythematosus, TBM-Tuberculous meningitis, p <0.05 was considered significant.

Kaplan Meier Survival Analysis estimated the mean time to development of hyperglycaemia as 19.57 days (95% CI, 17.06-22.08 days). Out of the 42 cases who developed hyperglycaemia, 34 developed the event within the first 3 days.

Out of 42 cases that developed hyperglycaemia, 2 patients developed diabetic ketoacidosis and required intravenous insulin infusion. All the other patients were managed with either oral hypoglycaemic agents or meal time insulin.

Table 2: Indications for steroid therapy

	Frequency	Percent
Adrenal insufficiency	1	0.9
AIHA	2	1.8
AOSD	1	0.9
APLA	1	0.9
COVID	52	46.4
Evans Syndrome	5	4.5
Gout	1	0.9
GPA	1	0.9
IBD	2	1.8
ITP	17	15.2
Membranous GN	1	0.9
MNM Secondary to RA	1	0.9
RA	10	8.9
SLE	14	12.5
SLE with SEC Sjogrens	1	0.9
TBM	2	1.8
Total	112	100.0

Table 3: Cox regression analysis of risk factors

		Cases n=42	Controls n=70	p value	Hazard Ratio	95% CI for HR	
						Lower	Upper
Age	Mean ± SD	37.857 ± 10.1994	38.957 ± 12.7216	0.328	0.984	0.954	1.016
Sex	n(%)	28 (66.7%)	26 (37.1%)	0.039	2.020	1.037	3.933
Family h/O DM	n(%)	26 (61.9%)	18 (25.7%)	0.011	2.469	1.234	4.942
HbA1C	Mean ± SD	5.579 ± 0.6513	5.649 ± 0.6513	0.103	0.645	0.381	1.093
BMI	Mean ± SD	25.768 ± 3.571	22.387 ± 3.058	0.014	1.121	1.023	1.228
Equivalent Dose	Median & IQR	200 (60-1250)	100 (40-200)	0.051	1.001	1.000	1.001

SD- Standard deviation, H/O- History of, F- Females, DM- Diabetes Mellitus, HbA1c- Glycosylated Hemoglobin, BMI- Body Mass Index, CI- Confidence interval, IQR- Inter quartile range, p <0.05 was considered significant.

DISCUSSION

Steroids are used in clinical practice for a multitude of conditions and the dose of steroid administered depends on disease activity. In this study of 112 patients, 42 cases (37.5%) developed hyperglycaemia during the period of study. Of these 58 (51.8%) were males, 54 (48.2%) were females. In a similar study done by Katsuyama *et al.* (2015) the incidence of steroid induced hyperglycemia was 65.6%. The incidence of steroid induced hyperglycaemia ranged from 1-53% in various studies conducted (Ha *et al.*, 2011).

In our study the proportion of females (66.7%) who developed hyperglycaemia was higher than males (33.3). These results differed from the study done by Braithwaite *et al.,* (1998) in which no significant association between gender and development of event was reported.

The most frequent indication for steroid therapy in our study was COVID-19. 52 patients (46.4%) received steroids for management of COVID-19, as the study was conducted during the period of the pandemic. Out of these, 12 patients (23.07%) developed hyperglycaemia. Steroid therapy is one of the mainstays of treatment for patients with moderate to severe COVID-19 disease and has shown significant mortality benefit. COVID -19 has been shown to cause new onset diabetes and severe metabolic complications of diabetes, including diabetic ketoacidosis and hyperosmolarity in a few studies and this could be because of the potential diabetogenic effect of the virus (WHO, 2011). However, our study did not study the relationship between COVID-19 and impaired glucose tolerance and attributed all the cases which developed hyperglycaemia to the use of steroids.

Out of the cases only 17(40.4%) had fasting hyperglycaemia indicating that post prandial hyperglycaemia was a more sensitive indicator. There was no significant difference in the mean HbA1c between the two groups.(p-0.562). Katsuyama *et al.* (2015) in their study found that, a higher HbA1c level ≥6% was a risk factor for the development of hyperglycaemia and that this might reflect underlying impaired glucose intolerance. The finding in our study might have underestimated HbA1c because of the high proportion of cases of anaemia secondary to ITP, haemolytic anaemia and autoimmune diseases like SLE. (Miyawaki *et al.*, 2017)

Age was not found to be a risk factor in our study (HR: 0.98). The relationship between increasing age and increasing insulin resistance is well documented. A study by Katsuyama *et al.* (2015) showed that the risk of developing diabetes more than doubles in elderly patients who are started on corticosteroids.

In our study, patients with family history of diabetes mellitus were found to be at 2.53 times at higher risk of developing the event when compared to patients with no such history Henriksen *et al.* (1997) reported in their study that the insulin resistance induced by dexamethasone caused impaired glucose tolerance in genetic relatives of type 2 diabetes mellitus, who had impaired beta cell function prior to steroid exposure. This probably implies that patients with a family history of diabetes mellitus already have impaired beta cell function and thus they are unable to enhance their insulin response in order to match the drug induced insulin resistance state.

The relationship between the metabolic syndrome and insulin resistance is well documented, thus obesity can contribute to the development of steroid induced hyperglycaemia. Patients with high BMI were found to have a 12% higher risk of developing hyperglycemia than those with a normal BMI (HR: 1.12). One case with BMI more than 27.5 kg/m2 developed DKA during the hospital stay and required intravenous insulin infusion. Iwamoto *et al.* (2004) in their study found BMI to be an independent risk factor for the development of hyperglycaemia. Additionally in our study, a history of the subject's level of physical activity was taken and they were catergorised into an active, moderate or sedentary lifestyle (Tokyo: Ministry of Health, Labour and Welfare of Japan; 2006). It was observed that, the group of patients who developed hyperglycaemia tended to have a more sedentary lifestyle compared to the group of patients who did not develop an event (p-0.004).

In this study, 32.1% female patients in the cases group had a history of gestational diabetes mellitus, compared to 15.4% in the control group (p - 0.150). Females with a personal history of GDM were found to have a 1.69 times more risk of developing hyperglycaemia, however it was statistically not significant. (HR: 1.69, p value- 0.19). Suh and Park (2017) in his review article listed a personal history of gestational diabetes mellitus as a risk factor for steroid induced hyperglycaemia.

The median equivalent dose of prednisolone administered in the cases group was 200 mg and in the control group was 100 mg (p- 0.001). High dose pulse methyl prednisolone (750-1250mg of equivalent dose of prednisolone) was administered to 21 patients. Of them, 13 developed hyperglycaemia, indicating that high doses of steroids for a short period can cause significant

hyperglycaemia. Clore and Thurby-Hay (2009) found dose to be a strong predictor of diabetes induction. Liu *et al.* (2014) performed a dose response study where he found that a larger dose of corticosteroid caused a greater reduction in insulin sensitivity.

The mean time to the development of event was 19.5 days. Out of 42 cases, 34 (80.9%) reported hyperglycaemia in the first three days of steroid therapy. Gonzalez-Gonzalez *et al.* (2013) found the incidence of hyperglycaemia was more common in the second and fourth week. The time to development of hyperglycaemia depends on the type, dose and frequency of the steroid administered.

LIMITATIONS

Patients older than 60 years weren't included in the study and this might have underestimated the incidence of hyperglycaemia. This study did not take into account the different types of steroids administered. Prednisolone is an intermediate acting steroid and dexamethasone has a more prolonged duration of action and this might have an effect on the timing of hyperglycaemia. The proportion of patients with anaemia in this study could have underestimated the value of the HbA1c, thus masking underlying glucose intolerance.There were only 13 female patients with a past history of gestational diabetes. This small number is insufficient to assess GDM as an independent risk factor and further studies are required in this area with a larger population.

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