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Research Article

Assessing the Impact of Usage of Steroids among Newly Detected Diabetes Patients in a Study among COVID-19 Patients across India

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Abstract

Background: There is a bidirectional relationship between COVID 19 and diabetes. New-onset diabetes and severe metabolic complications of pre-existing diabetes in patients with COVID 19 have been observed. Steroids are medications used for treatment of several diseases, including COVID-19. Its pharmacological action increases blood glucose and poses additional challenges in the management.

Aim: To study the impact of steroids on newly detected diabetes patients with a history of COVID-19 in a cohort group.

Methods: 2263 patients from 15 different sites across India were analysed following a specific eligibility criterion. The patients were segregated into three groups - No steroids, Low steroids [less than or equal to the median dose (50 mg)], and High steroids [greater than the median dose (50 mg)]. Two-way ANOVA was used to test the relationship between Diabetes status and Steroid usage.

Results: The steroid dosage for the management of COVID in the NDD received higher doses of steroids. All steroid doses were adjusted and standardized to prednisolone 5 mg. The average maximum doses of steroids used in the management of COVID for NDD was 86.6 mg/day. Within the NDD group, those who received a lower steroid dose had a higher HRCT score as compared to the No steroid and High steroid groups. Also, amongst all patients who did not receive steroids for management of COVID, NDD had a statistically higher HRCT score.

Conclusion: The prevailing hypothesis that increased application of steroids causes diabetes-like disease spectrums in patients recovering from COVID. The findings however require reconsidering steroid usage as the leading cause of COVID-induced diabetes.

Keywords: Steroids; Diabetes; COVID-19; SARS-CoV2; WHO; Diabetic ketoacidosis; Angiotensin-converting enzyme-2

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Introduction

COVID-19 which is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2), initially appeared in late 2019 in Wuhan, China, with the number of infections dramatically expanded throughout the world during the early 2020 [1]. There had been more than 600 million cases reported as per WHO worldwide [2]. The impact of COVID-19 went much beyond that of a contagious disease. COVID-19 had a direct influence on the health system as a communicable disease, as well as the power to alter global mortality and disease burden through its impact on non-communicable diseases [3]. The relationship between NCD risk factors and COVID-19 is unclear; however, multimorbidity, particularly renal, cardiovascular, and metabolic morbidity, is linked to an increased chance of COVID-19 positivity [4]. According to the evidence, COVID-19 is frequent in people with diabetes, hypertension, and cardiovascular disease, although the prevalence rate differs among different studies and countries. The world has expressed concern about a bidirectional relationship between these two health conditions, diabetes, in the first instance, is linked to a poor COVID-19 prognosis. In contrast, COVID-19 has been linked to both new-onset diabetes and severe complications of pre-existing diabetes, such as Diabetic Ketoacidosis (DKA) and hyperosmolarity.

Several hypotheses have been proposed to explain the rising rate of new-onset diabetes in COVID-19 patients. SARS-CoV-2 is thought to bind to Angiotensin-Converting Enzyme-2 (ACE-2) receptors found in adipose tissue, the lungs, the small intestine, the kidneys, and the pancreas. Following virus endocytosis, ACE-2 is significantly suppressed, resulting in angiotensin II overexpression, which may impair insulin secretion. Similarly, it has been proposed that direct entry of SARS-CoV-2 into pancreatic islet cells damages beta cells, which normally secrete insulin [5]. Both type 1 and type 2 diabetes, where insulin insufficiency plays a significant role, is affected by the damage of beta cells by SARS-CoV-2, likely *via.* ACE2 [6]. One reason for new-onset diabetes is that these patients may have had undiagnosed diabetes prior to admission, possibly as a result of recent weight gain due to changes in lifestyle and worsening of hyperglycaemia due to self-isolation, social distancing, decreased physical activity, and poor diets as a result of mental health issues. These lifestyle changes may result in insulin resistance, which may then activate inflammatory pathways, resulting in new-onset diabetes [7].

Steroids are medications that are used to treat a variety of diseases, including COVID-19 [8]. While it is lifesaving in several individuals with COVID-19 infection, its pharmacological action raises blood glucose and adds to the management challenges. Steroids raise blood sugar levels through a variety of mechanisms. From the evidence it has been noted that steroids increase the production of glucose from the liver by enhancing the effect of counter regulatory hormones [9], it increases insulin resistance and it may also reduce the uptake of glucose intake by muscles [10].

Aims and objectives

This study aims to understand the relationship between COVID-19, steroid use in Newly Detected Diabetes (NDD) rather than new-onset diabetes. The distinction between new-onset and NDD is more academic as it cannot be elucidated easily in a real-world setting, further undermined by the rush of the COVID-19 pandemic. Under the guidance of the American College of Physicians - India Chapter, a Real-World retrospective analysis of the experience of the severity of COVID and post-COVID symptoms was planned to gain practical insights from practicing physicians of the country with a strong focus on post-COVID hyperglycaemic states and diabetes detection.

Materials and Methods

A total of 15 sites participated in the study by invitation, and investigators in these sites had a large data repository of COVID-19 patients that they had managed during the first and second waves. All site investigators were explained the study aims and objectives, inclusion and exclusion criteria and were trained for the electronic data entry process by the investigator.

These 15 centers were based in 15 different geographical areas of India to ensure that the collected data would represent the country. The study was initiated after ethical clearance from all sites, and additional institutional review board clearance was sought in the institutional sites. All Indian patients above 18 years of age who had reported to the study sites for the management of COVID-19 were eligible to be included in the study. A positive report of COVID-19 through a Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR) test in the past was mandatory to confirm the diagnosis. In situations where complete data was unavailable at the site, the remaining data for these patients were captured when they reported to the center for regular care with their records.

The study was explained to the patients, and patients who agreed to participate shared their anonymous data and signed the informed consent enrolled in a consecutive sequence at each site. Patients who did not agree to sign the informed consent were excluded from the study.

The first wave of COVID-19 in India started in March 2020 and continued for 5 to 6 months, and the second wave started in April 2021 and continued for 2 to 3 months [15]. This study was conducted in June 2021, and the expected sample size was achieved by November 2021 (6 months). The statistical analysis was performed using SPSS and Python. The data is represented as mean for continuous and proportions for categorical data. ANOVA and Chi-square were used to compare the significance between patient groups on various parameters. T-test for means and proportions was used to test the significance between any two groups. The three groups were considered for these studies are specified in Figure 1.

The patients in the NDD group were further segregated into three groups - No steroids, Low steroids [less than or equal to the median dose (50 mg)], and High steroids [greater than the median dose (50 mg)]. Two-way ANOVA was used to test the relationship between Diabetes status and Steroid usage.

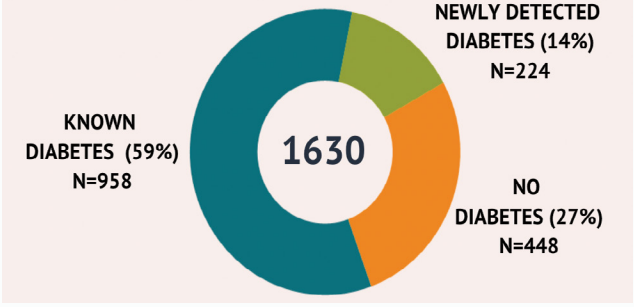

Figure 1: Patient break-up of the three groups: KD, ND and NDD.

Results

For the purpose of this study, three study groups were considered:

A. Known Diabetes (KD): patients with pre-existing Diabetes before they were diagnosed with COVID.

B. Non-Diabetes (ND): patients who didn't have diabetes before and remained with no diabetes even after the treatment of COVID 19.

C. Newly Detected Diabetes (NDD): patients who were detected with hyperglycemia for the first time during or after the treatment of COVID 19 and were being managed for diabetes at the time of the survey.

Flow chart - sample size (Figure 2)

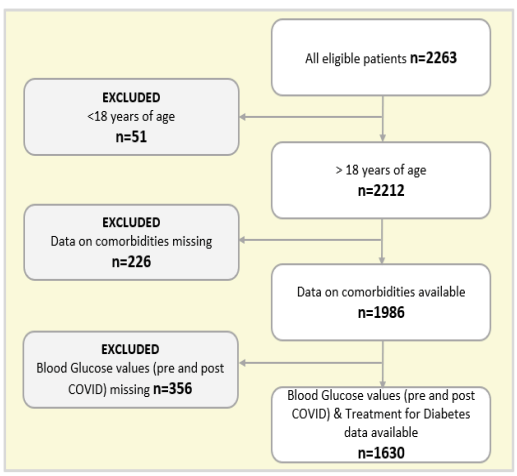

Figure 2: Execution flow chart for the selection of the sample size.

Total Sample and study profiles

The average age of the study population was 50.4 years with minimum 19 and maximum 95 years. The gender distribution was 62% (n=1012) males and 38% (n=618) females (Table 1).

There was 3 study groups KD (Known Diabetes - n=958), NDD (Newly Detected Diabetes, n=224) and ND (Non-Diabetes, n=448). KD was 58.8%, the NDD was 13.7% and, ND was 27.5% respectively of the total sample size.

Patients in ND with a mean age of 45.1 years (43.8 to 46.5 years) were younger than KD with a mean age of 52.7 years (51.9 to 53.5 years) and NDD with a mean age of 50.8 years (48.6 to 52.9 years). The differences in age between the study groups was statistically significant with a p value <0.001. The gender distribution in the three groups was consistent with the total sample (62.1% male) for all the three study groups with around 60% of the patients being male in each group.

Assessing the association between strength of the steroid with diabetes groups on HRCT score, it was found that the average HRCT score for NDD was significantly higher (15.8/25) than that of KD (11.1/25) and ND (11/25). The proportion of severe disease (HRCT ≥ 18) was more among NDD (48%) as compared to KD (15%) and ND (16%). The NDD group received higher doses of steroids as compared to the other two groups Figure 3. NDD group received a higher strength of steroids as 86.6 mg, while KD and ND were comparatively lower at 67.5 mg and 62.4 mg respectively. The duration of days for steroid usage in NDD was 8.8 days, while for KD was 9.4 days and ND was 10 days (Table 1).

Within each of the steroid groups, NDD had a significantly HRCT score (Figure 3). The NDD group average HRCT value was higher (17.2) in Low steroids group compared to No and High steroids groups with average values 13.2 and 14.9 respectively. Looking at the association of steroid usage with the severity in the NDD group, low steroid had a higher HRCT as compared to the high steroid group, thereby highlighting that the severity in our study is not linked to the steroid usage.

Discussion

Diabetes patients appear to have COVID-19 more frequently and more severely. On the pathogenesis of diabetes, COVID-19 may have an impact. Blood glucose management is crucial for everyone, not just COVID-19 patients. In the modern era, innovations like telemedicine are helpful in treating diabetes patients. Alterations to glucose homeostasis, an uptick in cytokine production that triggers the cytokine storm and increased oxidative stress are only a few of the pathogenic connections between DM and COVID-19. The immune system is altered in people with diabetes, and their risk of infection is raised by elevated ACE-2 expression as well as other enzymes like furin and altered ACE-2 expression. In hyperglycaemic people, inherent pathogenic pathways enhance the risk of infection and are responsible for more tissue damage and mortality. The rate of viral invasion may be accelerated by ACE-2 expression brought on by anti-glycemic medication [11]. Our study highlighted that severity of COVID was highest in NDD group so is the dosage of steroids in our study. On further analysis, to understand each of the sub groups and dosage levels, it is seen that in the NDD group the low steroid group had higher COVID severity, putting forward that severity of the disease might have not been associated with the steroid dose in patients. In a systematic review it was assessed whether inhaled corticosteroids are effective and safe in the treatment of COVID-19. There was moderate confidence information that inhaled corticosteroids likely reduce the combined endpoint of hospital admission or mortality and increase the remission of all initial symptoms at day 14 in individuals with confirmed COVID-19 and mild symptoms that are able to utilise inhaler devices. Evidence with a low degree of certainty indicates that corticosteroids may shorten the time it takes for symptoms to go away and have little to no effect on all-cause mortality up to day 30. Because significant adverse events were documented in different ways in different trials, it is unknown whether inhaled corticosteroids increase or decrease serious adverse events. Inhaled corticosteroids may reduce infections, according to low-certainty evidence [12]. According to a study conducted by Wagner et al. [13] evaluated the effectiveness and safety of systemic corticosteroids in the treatment of COVID-19 patients, these medications likely marginally lower all-cause mortality in patients who are hospitalised due to symptomatic COVID-19. There may also be a decline in days without a ventilator, according to research with low certainty. A systematic review conducted by Cruciani et al. [14] aimed to analyse the corticosteroids use for the treatment of COVID-19 it was reported that in critically ill COVID-19 patients, corticosteroids have been shown to be more effective than standard of care in reducing mortality and disease progression without raising the risk of adverse events. This finding has a moderate degree of certainty. In a retrospective analysis conducted by Tortajada et al. [15], the therapeutic efficacy of corticosteroid treatment in individuals with mild to severe COVID-19 was evaluated. The findings demonstrated that patients who required NIV, high-flow

Table 1: Demographics and Steroid details.

		Over all	KD	Diabetes Groups NDD	ND	P-value
Age (years), mean (CI)	n=	1630	958	224	448	<0.001
		50.4 (50-51)	52.7 (52-54)	50.7 (49-53)	45.1 (44-47)	
Age groupings, n (%)	15-24 years	31 (1.9)	3 (0.3)	8 (3.6)	20 (4.5)	<0.001
	25-34 years	228 (14.0)	80 (8.4)	44 (19.6)	104 (23.2)	
	35-44 years	331 (20.3)	191(19.9)	30 (13.4)	110 (24.6)	
	45-54 years	395 (24.2)	244 (25.5)	48 (21.4)	103 (23.0)	
	55-64 years	331 (20.3)	236 (24.6)	36 (16.1)	59 (13.2)	
	65+ years	314 (19.3)	204 (21.3)	58 (25.9)	52 (11.6)	
Gender, n (%)	Male	1012 (62.1)	609 (63.6)	134 (59.8)	269 (60.0)	0.337
	Female	618 (37.9)	349 (36.4)	90 (40.2)	179 (40.0)	
HRCT, mean (SD)	n=	1052	555	164	333	<0.001
		11.8 (5.5)	11.1 (5.1)	15.8 (5.6)	11.0 (5.2)	
Strength of steroid (mg/per), mean (SD)	n=	1184	685	185	314	0.007
		69.1 (85.6)	67.5 (83.3)	86.6 (113.5)	62.4 (69.0)	
Duration of the steroids (days), mean (SD)	n=	1037	549	177	311	0.048
		9.5 (5.2)	9.4 (5.5)	8.8 (4.7)	10.0 (5.0)	

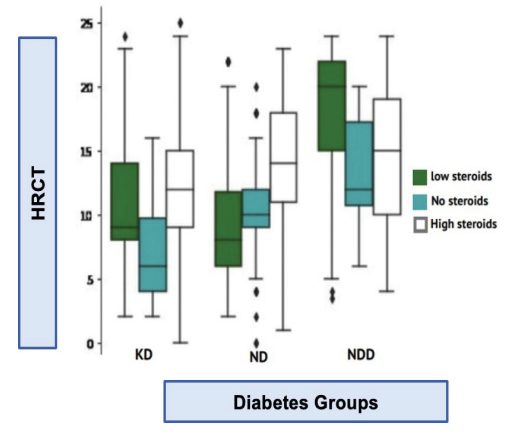

Figure 3: HRCT vs Steroids X Diabetes groups.

oxygen, or FiO_2>0.40 and received corticosteroids had a lower risk of in-hospital death or ICU admission than those who did not. Patients who required low-flow oxygen and had a FiO_2 below 0.40 did not have a statistically significant reduction for the same objective.

Conclusion

In the treatment of COVID-19, steroids are proven to be life-saving medications. Steroids significantly contribute to the decline in COVID-19 patient deaths while they are hospitalised. But still there is lack of evidence so more research and analysis are essential for the physicians to make better clinical decisions. The prevailing hypothesis is that increased application of steroids causes diabetes-like disease spectrums in patients recovering from COVID-19. The findings however require reconsidering steroid usage as the leading cause of COVID-induced diabetes. Therefore, further larger studies and more prospective metabolic investigations are needed to determine a definitive correlation, etiology, possible risk factors, prognosis, and treatment for NDD post-COVID-19 infection.

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