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An Association Between Different Doses of Inhaled Corticosteroids and Glycaemic Status in Patients with Chronic Obstructive Pulmonary Disease

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Abstract: Introduction: Inhaled corticosteroids effective medications for the treatment of asthma. Higher doses of inhaled fluticasone (1000 µgm / day) are commonly used in COPD. Such high doses have been associate with significant systemic effects such as pneumonia, glaucoma, cataracts, adrenal suppression and accelerated bone turnover. Aim of the study: The aim of the study was to evaluate the association between different doses of inhaled corticosteroids (Fluticasone Propionate µgm / day) and glycaemic status in Patients with Chronic Obstructive Pulmonary Disease. Material & Methods: This was a cross-sectional analytical study. This study was conducted at the department of Internal Medicine in Bangobandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, during May, 2016-April, 2017. The protocol of this study was approved by IRB and ethical committee. A total of 80 patients with COPD were included in this study, of them clinically diagnosed 40 consecutive COPD patients who were receiving both bronchodilator & inhaled corticosteroids were recruited as case group and clinically diagnosed 40 consecutive COPD patients receiving only bronchodilator without inhaled corticosteroid/systemic steroid were recruited as control, group. Spirometry was done for confirmation and staging of COPD according to GOLD at indoor and OPD patients of Department of Internal Medicine, BSMMU. Results: In case group, the inhaled corticosteroid dose (5000) was counted 02 (5%) and the mean of FPG value was 6.25±1.34, the inhaled corticosteroid dose (1000) was counted 27 (67.5%) and the mean of FPG value was 5.7±1.58, the inhaled corticosteroid dose (2000) was counted 11 (27.5%) and the mean of FPG value was 6.58±2.24. The total FPG mean of the doses was 5.97±1.78. Among case group according to inhaled corticosteroid dose in case group, the inhaled corticosteroid dose (500) was counted 02 (5%) and the mean of 2HABF value was 9.65±3.18, the inhaled corticosteroid dose (1000) was counted 27 (67.5%) and the mean of 2HABF value was 8.71±2.84, the inhaled corticosteroid dose (2000) was counted 11 (27.5%) and the mean of 2HABF value was 9.51±2.9. The total mean of 2HABF value of the doses was 8.98±2.82. In case group, the inhaled corticosteroid dose (500) was counted 02 (5%) and the mean of HbA1C value was 5.85±1.06, the inhaled corticosteroid dose (1000) was counted 27 (67.5%) and the mean of HbA1C

value was 6.07±0.7, the inhaled corticosteroid dose (2000) was counted 11 (27.5%) and the mean of HbA1C value was 6.7±0.74. The total mean of HbA1C value of the doses was 6.23±0.77. Conclusion: We had found that 32% of cases and 7.5% of control group were diagnosed as diabetic when fasting plasma glucose taken into account, while in case of 2 hours after breakfast plasma sugar the number were 32.5% and 10% respectively and in case of HbA1c the number were 23.5% and 10% respectively.

Keywords: Inhaled Corticosteroids, Glycaemic Status, COPD, Inhaled Corticosteroid Dose

1. Introduction

Inhaled corticosteroids are generally used as effective medications for the treatment of asthma. Their effectiveness in treating chronic obstructive pulmonary disease are still up to debate [1], as these drugs are primarily recommended for more severe COPD cases, with frequent exacerbations [2]. Nevertheless, they are increasingly being used even in patients with less severe disease [3]. Moreover, higher doses of inhaled fluticasone (1000 µgm / day) are commonly used in COPD [4]. Such high doses can be associated with significant long term systemic effects such as pneumonia, glaucoma, cataracts, adrenal suppression and accelerated bone turnover [5]. The possible association between inhaled corticosteroids and worsening of diabetes is still being studied. This issue is particularly relevant to patients with COPD, as it is a major cause of chronic disability, the prevalence of which increases steadily with age, similarly to type 2 diabetes. Moreover, a higher prevalence and incidence of type 2 diabetes is being observed in patients with COPD [6]. As corticosteroid medications used in the treatment of COPD are often associated with deterioration in glycaemic control, the co-existence of these 2 chronic conditions among the elderly becomes important. Various randomized trials were conducted in COPD, but although there were some adverse effects, no excess rate of adverse events of diabetes associated with inhaled corticosteroid use was reported [7]. A recent observational study found that inhaled corticosteroid use was not associated with change in serum glucose concentration in patients who do not also have diabetes, but a change was observed in a dose response manner in patients with existing diabetes [8]. The dose-response effects of inhaled corticosteroid use observed on both the incidence and progression of diabetes are particularly important in the risk-benefit equation for patients with COPD [8]. Despite the effectiveness of inhaled corticosteroids on the treatment of asthma, their effectiveness in treating COPD is controversial. Long-acting bronchodilator is recommended in earlier stages of COPD, but as inhaled corticosteroids are now commonly combined in a single device with this, it has resulted in inhaled corticosteroids now being used by over 70% of COPD patients. These combined medications can contain as high of a dose as 1000 µg of fluticasone per day. Studies focusing on the effect of inhaled corticosteroid on COPD patients with induction of diabetes are limited and no such investigation has been conducted among the Bangladeshi population. Considering the fact that proper glycaemic status is an important factor for better response to treatment among COPD patients, which may lead to better outcome in patients' physical health, overall outcome and mortality and morbidity. On the other hand, as a developing country with high burden of DM and COPD and no previous study on effects of glycaemic status has been conducted in Bangladesh, this Cross-sectional analytical study of COPD patients attending at Internal Medicine department of BSMMU was conducted to assess blood sugar statuses who are taking inhaled corticosteroids.

2. Objectives

a) General objective:

To see any association between different doses of inhaled corticosteroids (Fluticasone Propionate µgm / day) and glycaemic status in patients with COPD.

b) Specific Objectives:

1. To determine the effect of inhaled corticosteroid on glycaemic status in patients with COPD.
2. To determine the fasting plasma glucose (mmol/L) & 2 hrs after breakfast plasma glucose (mmol/L) of COPD patients on ICS.

3. Methodology and Materials

This was a cross-sectional analytical study. This study was conducted at the department of Internal Medicine in Bangobandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, during May, 2016-April, 2017. The protocol of this study was approved by IRB and ethical committee. A total of 80 patients with COPD were included in this study, of them clinically diagnosed 40 consecutive COPD patients who were receiving both bronchodilator & inhaled corticosteroids were recruited as case group and clinically diagnosed 40 consecutive COPD patients receiving only bronchodilator without inhaled corticosteroid/systemic steroid were recruited as control, group. Spirometry was done for confirmation and staging of COPD according to GOLD at indoor and OPD patients of Department of Internal Medicine, BSMMU. *Sample size was calculated by using the following formula*: (Patients per group (n)=$f(\alpha,\beta) \times 2 \times \frac{(SD)^2}{d^2}$, (when comparing two independent group means) where, n=sample size in each group, f (α; β)=10.5 for 90% d^2 power with 5% (0.05) significance, d=3 (we wish to detect difference between two means), SD=4 (Pooled standard deviation of each group) *Using the above formula the expected sample size was calculated as 76. But due to time constrains sample size was finally fixed as 40 in each group. Samples were*

selected using purposive sampling technique through inclusion and exclusion criteria of this study. A predesigned questionnaire for socio-demographic and other variables and a check list for collection of disease information and measurement were *used for data collection. Face to face interview was conducted by the Researcher himself.* In case of illiterate patient data was collected from the patient's attendant. The collected data were analyzed and performed by statistical package for social science (SPSS), version-20. All collected data were checked and verified thoroughly to reduce inconsistency and for omission and improbabilities. Categorical variables were compared by chi-square test. In case group, association of glycaemic status with different doses of ICS was seen by Pearson's correlation coefficient. The level of significance was set at 5% and p-value of < 0.05 was considered as significant.

Inclusion Criteria

1. Case:
   a. Age more than 40 years
   b. Gender (male & female)
   c. Patients on inhaled bronchodilator & corticosteroid therapy for > 6 months
2. Control:
   a. Age more than 40 years
   b. Gender (male & female)
   c. Patients who were not taking inhaled corticosteroid/systemic steroid during his /her illness
   d. Exclusion Criteria
3. Patients with prior diagnosis of pre- diabetes & diabetes mellitus with COPD
4. Critically ill patients

4. Results

A total of 80 patients with COPD were included in this study, of them clinically diagnosed 40 consecutive COPD patients who were receiving both bronchodilator & inhaled corticosteroids were recruited as case group and clinically diagnosed 40 consecutive COPD patients receiving only bronchodilator without inhaled corticosteroid/systemic steroid were recruited as control, group. Table 1 shows the age distribution of the control group. The mean age of case group was 65.65±7.63 years, on the other hand, the mean age of control group was 53.85±7.9 years (p=0.841). Table 4 shows the gender distribution of both the case and control groups having corticosteroids. Among the total studied patients, male was 69 (86.30%), and female were 11 (13.70%). Total underweight (<18.5) were 23 (28.80%), normal weight was 53 (66.30%), over weight (25.0-29.9, were 03 (3. 80%), obese was 01 (2,5%) in both the groups. Total rural residences were 46 (57.5%), urban residences were 34 (42.5%) in both the cases (Table 6). Total illiterate was 31 (38.80%), primary level was 12 (15%), secondary level was 11 (13.80%), higher secondary level was 17 (21.30%), bachelor or above was 09 (11.30%) in both the cases *(*Table 7*). Total service was 22 (27.5%), business was 29 (36.30%) in both the cases, retired were 15 (18.80%), unemployed were 14 (17.5%) in both the groups (Table 8).* Total monthly income*, (*< 10000 BDT) were 17 (21.30%), monthly income (10000 -30000BDT) were 30 (37.5%) in both the groups, monthly income (>30000BDT) were 33 (41.30%) in both the groups *(Table 9). Total smokers were 60 (75%), non-smokers were 12 (15%), ex-smokers were 08 (10%) in both the groups (Table 10).* Total duration of symptom (<5 years) were 25 (31.30%), duration of symptom, (6-10 years) were 40 (50%), duration of symptom, (11-15 years) were 15 (18.80%) in both the groups *(Table 11*). *(Table 12):* Stages of COPD between case and control groups. In case group, stage (i) was 00 (00%), and in control group, stage (i) was 07 (17.55). The total stage (i) was 07 (8.80%) in both the groups. In case group, stage (ii) was 18 (45%), and in control group followed the same 18 (45%). The total of stage (ii) was 36 (45%) in both the cases. In case group, stage (iii) was 20 (50%), and in control group, stage (iii) was 14 (35%). The total stage (iii) was 34 (42.5%). In case group, stage (iv) was 02 (05%), and in control group stage (iv) was 01 (2.5%). The total stage (iv) was 03 (3.80%) in both the groups. (Table 13) shows the distribution of FPG (mmol/L) value between case and control groups. In case group, DM (>7) was 13 (32.5), and in control group, DM (>7) was 03 (7.5%). The total DM (>7) was 16 (20%) in both the groups. In case group, IFG (6.1-6.9 was 02 (5%), and in control IFG (6.1-6.9 was 04 (10%) which was double than case group. The total IFG (6.1-6.9 was 06 (7.5%) in both the cases. In case group, Normal (< 6.1) was 25 (62.5%), and in control group, Normal (< 6.1) was 33 (82.5%). The total Normal (< 6.1) was 58 (72.5) in both the groups. (Table 14) shows the comparison of mean FPG value between case and control groups. In case group, the mean FPG-value was 5.97±1.78 On the other hand, in control group, the mean FPG-value was 5.14±0.93 (p=0.01). (Table 15) shows the mean of FPG value among case group according to inhaled corticosteroid dose. In case group, the inhaled corticosteroid dose (5000) was counted 02 (5%) and the mean of FPG value was 6.25±1.34, the inhaled corticosteroid dose (1000) was counted 27 (67.5%) and the mean of FPG value was 5.7±1.58, the inhaled corticosteroid dose (2000) was counted 11 (27.5%) and the mean of FPG value was 6.58±2.24. The total FPG mean of the doses was 5.97±1.78. (Table 16) shows the mean of 2HABF value among case group according to inhaled corticosteroid dose in case group, the inhaled corticosteroid dose (500) was counted 02 (5%) and the mean of 2HABF value was 9.65±3.18, the inhaled corticosteroid dose (1000) was counted 27 (67.5%) and the mean of 2HABF value was 8.71±2.84, the inhaled corticosteroid dose (2000) was counted 11 (27.5%) and the mean of 2HABF value was 9.51±2.9. The total mean of 2HABF value of the doses was 8.98±2.82. (Table 17) shows the mean of HbA1C value among case group according to inhaled corticosteroid dose. In case group, the inhaled corticosteroid dose (500) was counted 02 (5%) and the mean of HbA1C value was 5.85±1.06, the inhaled corticosteroid dose (1000) was counted 27 (67.5%) and the mean of HbA1C value was 6.07±0.7, the inhaled corticosteroid dose (2000) was counted 11 (27.5%) and the mean of HbA1C value was 6.7±0.74. The

total mean of HbA1C value of the doses was 6.23±0.77. (Table 18) shows the mean of FPG, 2HABF and HbA1C value among case group according to duration of inhaled corticosteroid usage. The duration of ICS usage (1-3) years was counted 27 (67.5%), and the mean of FPG value was 6.11±2, 2HABF value was 9.4±3.03 and HbA1C value was 6.3±0.83. The duration of ICS usage (4-6) years was counted 13 (32.5%), and the mean of FPG value was 5.67±1.21, 2HABF value was 8.11±2.18 and HbA1C value was 6.1±0.62. The total mean of FPG value was 5.97±1.78, 2HABF value was 8.98±2.82 and HbA1C value was 6.23±0.77. (Table 19) shows mean of FPG, 2HABF and HbA1C value among the studied patients according to smoking status. Among the studied patients, smokers were 60 (75%), and the mean of FPG value was 5.55±1.41, 2HABF value was 8.48±2.43 and HbA1C value was 5.99±0.67. Non-smokers were 12 (15%), and the mean of FPG value was 5.99±2, 2HABF value was 7.9±2.85 and HbA1C value was 6.15±0.88. Ex-smokers were 08 (10%), and the mean of FPG value was 4.92±0.68, 2HABF value was 6.77±1.9 and HbA1C value was 5.78±0.64. The total mean of FPG value was 5.55±1.47, 2HABF value was 8.23±2.48, and HbA1C value was 6±0.7 counted among the studied patients on the basis of smoking status which signified glycaemic control according to smoking status.

Table 1. *Age distribution of the studied patients (control group) (n=40).*

Age group	Frequency	%
40-49	15	37.5
50-59	15	37.5
60 or above	10	25
Total	40	100

Table 2. *Age distribution of the studied patients (case Group) (n=40).*

Age group	Frequency	%
40-49	09	22.4
50-59	16	40.00
60 or above	15	37.5
Total	40	100

Table 3. *Comparison of mean age between case and control groups (n=80).*

Group	N	Mean	SD	p-value
Case	40	65.65	7.63	0.841
Control	40	53.85	7.9	

Table 4. *Gender Distribution of the studied patients (n=80).*

Gender		Patients having corticosteroids		Total
		Case	Control	
Male	Count	34	35	69
	Percentage	85.00%	87.50%	86.30%
Female	Count	6	5	11
	Percentage	15.00%	12.50%	13.70%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 5. *Distribution of BMI of the studied patients having corticosteroid or not (n=80).*

BMI		Case	Control	Total
Under weight (<18.5)	Count	13	10	23
	Percentage	32.50%	25.00%	28.80%
Normal (18.5-24.9)	Count	26	27	53
	Percentage	65.00%	67.50%	66.30%
Over Weight (25.0-29.9)	Count	0	3	3
	Percentage	0%	7.50%	3.80%
Obese (30-39.9)	Count	1	0	1
	Percentage	2.50%	0.00%	2.50%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 6. *Residential status of the studied patients (n=80).*

Residence		Case	Control	Total
Rural	Count	20	26	46
	Percentage	50.00%	65.00%	57.50%
Urban	Count	20	14	34
	Percentage	50.00%	35.00%	42.50%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 7. *Educational status of the studied patients (n=80).*

Educational status		Case	Control	Total
Illiterate	Count	13	18	31
	Percentage	32.50%	45.00%	38.80%
Primary level	Count	7	5	12
	Percentage	17.50%	12.50%	15.00%
Secondary level	Count	8	3	11
	Percentage	20.00%	7.50%	13.80%
Higher secondary level	Count	8	9	17
	Percentage	20.00%	22.50%	21.30%
Bachelor and above	Count	4	5	9
	Percentage	10.00%	12.50%	11.30%
	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 8. *Occupation of the studied patients (n=80).*

Occupation		Case	Control	Total
Service	Count	14	8	22
	Percentage	35.00%	20.00%	27.50%
Business	Count	10	19	29
	Percentage	25.00%	47.50%	36.30%
Retired	Count	9	6	15
	Percentage	22.50%	15.00%	18.80%
Unemployed	Count	7	7	14
	Percentage	17.50%	17.50%	17.50%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 9. *Monthly income of the studied patients (n=80).*

Monthly income (BDT)		Case	Control	Total
< 10000	Count	7	10	17
	Percentage	17.50%	25.00%	21.30%
10000 -30000	Count	15	15	30
	Percentage	37.50%	37.50%	37.50%
> 30000	Count	18	15	33
	Percentage	45.00%	37.50%	41.30%
Total count		40	40	80
Total percentage		100.00%	100.00%	100.00%

Table 10. *Smoking status of the studied patients (n=80).*

Participants' smoking status		Case	Control	Total
Smoker	Count	31	29	60
	Percentage	77.50%	72.50%	75.00%
Non- smoker	Count	6	6	12
	Percentage	15.00%	15.00%	15.00%
Ex-smoker	Count	3	5	8
	Percentage	7.50%	12.50%	10.00%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 11. *Duration of symptoms between case and control groups (n=80).*

Duration		Case	Control	Total
<5 years	Count	8	17	25
	Percentage	20.00%	42.50%	31.30%
6-10 years	Count	23	17	40
	Percentage	57.50%	42.50%	50.00%
11-15 years	Count	9	6	15
	Percentage	22.50%	15.00%	18.80%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 12. *Stages of COPD between case and control groups (n=80).*

Stages		Case	Control	Total
i	Count	0	7	7
	Percentage	0.00%	17.50%	8.80%
ii	Count	18	18	36
	Percentage	45.00%	45.00%	45.00%
iii	Count	20	14	34
	Percentage	50.00%	35.00%	42.50%
iv	Count	2	1	3
	Percentage	5.00%	2.50%	3.80%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 13. *Distribution of FPG value between case and control groups (n=80).*

FPG (mmol/L)		Case	Control	
DM (>7)	Count	13	3	16
	Percentage	32.50%	7.50%	20.00%
IFG (6.1-6.9)	Count	2	4	6
	Percentage	5.00%	10.00%	7.50%
Normal (< 6.1)	Count	25	33	58
	Percentage	62.50%	82.50%	72.50%
Total	Count	40	40	80
	Percentage	100.00%	100.00%	100.00%

Table 14. *Comparison of mean FPG value between case and control groups (n=80).*

		N	Mean	Std. Deviation	P Value
FPG-value	Case	40	5.97	1.78	<0.01
	Control	40	5.14	0.93	

Table 15. *Mean of FPG value among case group according to inhaled corticosteroid dose (n=40).*

Dose	Mean FPG	N	Std. Deviation	%
500	6.25	2	1.34	5.00%
1000	5.7	27	1.58	67.50%
2000	6.58	11	2.24	27.50%
Total	5.97	40	1.78	100.00%

Table 16. *Mean of 2HABF value among case group according to inhaled corticosteroid dose (n=40).*

Dose	Mean of 2HABF	N	Std. Deviation	%
500	9.65	2	3.18	5.00%
1000	8.71	27	2.84	67.50%
2000	9.51	11	2.9	27.50%
Total	8.98	40	2.82	100.00%

Table 17. *Mean of HbA1C value among case group according to inhaled corticosteroid dose (n=40).*

Dose	HbA1C level	N	Std. Deviation	%
500	5.85	2	1.06	5.00%
1000	6.07	27	0.7	67.50%
2000	6.7	11	0.74	27.50%
Total	6.23	40	0.77	100.00%

Table 18. *Mean of FPG, 2HABF and HbA1C value among case group according to duration of inhaled corticosteroid usage (n=40).*

ICS duration		FPG	2HABF	HbA1C
1-3 year	Mean	6.11	9.4	6.3
	N	27	27	27
	Std. Deviation	2	3.03	0.83
	Percentage among case	67.50%	67.50%	67.50%
4-6 years	Mean	5.67	8.11	6.1
	N	13	13	13
	Std. Deviation	1.21	2.18	0.62
	Percentage among case	32.50%	32.50%	32.50%
Total	Mean	5.97	8.98	6.23
	N	40	40	40
	Std. Dev	1.78	2.82	0.77
	Percentage among case	100.00%	100.00%	100.00%

Table 19. *Mean of FPG, 2HABF and HbA1C value among the studied patients according to smoking status (n=80).*

Participants smoking status		FPG value	2HABF value	HbA1C value
Smoker	Mean	5.55	8.48	5.99
	N	60	60	60
	Std. Deviation	1.41	2.43	0.67
Non-smoker	Mean	5.99	7.9	6.15
	N	12	12	12
	Std. Deviation	2	2.85	0.88
Ex-smoker	Mean	4.92	6.77	5.78
	N	8	8	8
	Std. Deviation	0.68	1.9	0.64
Total	Mean	5.55	8.23	6
	N	80	80	80
	Std. Deviation	1.47	2.48	0.7

5. Discussion

When compared to the oral or parenteral routes of administration, inhaled corticosteroids (ICS) are generally known to produce comparatively less adverse effects, and their effect on carbohydrate metabolism is less well recognized. Patients with COPD are known to have a higher risk of developing type 2 diabetes [12]. In this cross-sectional analytical study, total of 80 subjects was included for the study on the basis of inclusion and exclusion criteria, 40 of them were taken as case and 40 as age matched control. There was no defaulter or drop out cases, so finally 80 subjects were enrolled in this study, clinically diagnosed 40

consecutive COPD patients (50%) who were receiving both bronchodilator & inhaled corticosteroids were recruited as case. Clinically diagnosed 40 consecutive COPD patients (50%) receiving only bronchodilator without inhaled corticosteroid/systemic steroid were recruited as control. Both groups were well matched for age and other socio-demographic variables. There was no statistical difference in the mean age of both group which was 53.85±7.9 and 56±7.6 in control and case respectively. This finding were somewhat different from some previous other study done by Slatore et al [8] and Faul et al [9]. where mean age was somewhat more than our study group, that is 64 and 65.4 respectively. Spirometry was done for confirmation and staging of COPD according to GOLD at indoor and OPD patients of Department of Internal Medicine, BSMMU. ICS are considered an integral part of anti-inflammatory treatment in patients with asthma, although their effectiveness in COPD remains controversial [10]. In patients with COPD, the use of ICS is primarily recommended for severe disease and in those with frequent episodes of exacerbations [11]. In our study it is also found that significant number of GOLD stage 1 and 2 are using inhaled steroids which are not justified. Similar trend has found in most of the previous studies. Using a population-based study on COPD patients, we found that the use of inhaled corticosteroids is associated with a significant increase in the risk of incident of diabetes. The observed treatment-related changes in % N HbA1c in this study are consistent with another report of hyperglycemia and glucosuria in an asthmatic patient who took very high doses of inhaled FP at a dose of 2 mg/day; however, the mean increase resulting from FP therapy, relative to the individual's own baseline, is substantially smaller than in that individual case [12]. Socio-demographic characteristics of the study showed that among the cases 85% were males and 15% were females while in control group it was 87.5% and 12.5% respectively. A study done by Saltore et al [8] had found 97% of respondent were male. Most of the population belongs to male sex which is probably due to more smoking rate among male, this finding are somewhat similar to a previous study done by Faul et al. and Mirrakhimov et al [9], [13]. Among the cases 50% are from rural areas and 50% from urban areas where as in control group the rate is 65% and 35% respectively. This finding of equal number of cases from urban and rural areas signifies that burden of diseases and its prevalence is more than other countries which was prevailed by some other abroad studies where disease prevalence was more in urban area [14], [15] 32% in case group and 65% of patients in control group are those who ever never attend the school while only 10% in case and 12.5% in control group have completed their bachelors as well as masters level education whereas in a study done by Christopher et al [16], had shown that 62% of study population had completed their bachelors. This number signifies that this huge difference in educational status has a mammoth impact in occurrence of COPD. So improvement in educational status can helps in controlling future prevalence of COPD. 77.5% of the case and 72.5% of control population are indulging in smoking while only 15% from each group are non- smoker, these picture is somewhat different in the study done by Christofer et al [16], where the number of smoker in case and control group are 27% and 22% respectively. These signify the high disease burden among smoker. Proper education, awareness creating program, symposium, anti-smoking movement and strong stand of policy maker, all can improve this picture and can help in reducing future prevalence of the disease burden. In respect of occupation it is found that there is a large number of cases are service holder and businessman (35% and 20%), which is true for control group also (20% and 47.5%). Most of the cases are from higher socioeconomic background (45%), whereas in control group it is 37.5%. This demographic variable also differe from study done by Christofer et al [16]. They found that 89% of case population and 87% of control population are belongs to lower socio-economic group. But this figure is somewhat similar to study done by Kian et al [15], they had found that the number is 42.8% and 40.6% respectively. In 20% cases symptoms duration was less than 5 years, where as in control group it was 42.5%. And duration more than 11-15 years was 22.5% and 15% respectively. We had found that 32% of cases and 7.5% of control group were diagnosed as diabetic when fasting plasma glucose taken into account, while in case of 2 hours after breakfast plasma sugar the number were 32.5% and 10% respectively and in case of HbA1c the number were 23.5% and 10% respectively. The study done by Suissa et al [10] had shown that there is 34% incidence rate among ICS users whereas the study done by Chrostopher et al [16] had found no significance differences of incidences of diabetes among ICS users compared with non-ICS users. Among the most widely used, methylprednisolon is the one that worsens glycaemic control the most, followed by hydrocortisone. Deflazacort has less effect on glycaemic control. We cannot ignore the possible effect of inhaled corticosteroids on glycaemic control. Many patients follow an inhaled drugs schedule for their existent COPD. Although considered a safe treatment, some systemic effects have been described. Cataracts and suppression of the hypothalamic-pituitary-adrenal are possible effects when maximum dose are given [9]. In addition, some studies have shown [9] a significant increase (1.0%) in glycated hemoglobin and the persistence of glycosuria in patients who used high-dose inhaled fluticasone (2 mg / day). Other study [13], shows that high dose of inhaled corticosteroids is associated with small changes in glycaemic control that are detectable but not clinically relevant as they would not be a criterion to stop or change the treatment. An important concern is that Type II diabetes is asymptomatic in its early stages, and a notoriously under-treated and under-diagnosed disease. In our study it has shown that there is significant difference in fasting, post prandial and HbA1c in patients having inhaled corticosteroids compared to those on inhaled bronchodilators only. Together, these data support a link between ICS (in the doses employed in these studies) and new onset diabetes mellitus in COPD patients. Systemic corticosteroids are associated with insulin resistance and hyperglycaemia.

Therefore, it might be anticipated that inhaled corticosteroids, particularly at high doses, might also result in hyperglycaemia. Suissa et al [10], have reported, in a large nested case-controlled study, that ICS exposure was associated with an increase in the risks of diabetes onset and diabetes progression. However, others have only been able to show an effect of ICS on blood sugar in patients already treated for diabetes and Dendukuri et al [17], did not find any association of diabetes (identified by its treatment with medications) with the dispensing of ICS. The main limitation of these other studies was that they were observational in nature and could not account for measured and unmeasured factors that may have distorted the findings such as confounding by indication (i.e sicker patients with co-morbidities may have been more likely to have received ICS) or reverse confounding (i.e as sicker patients are more likely to have co-morbidities, ICS may have been avoided in such patients).

Limitations of the Study

There are some limitations in the present study that may have some potential impacts on the results. First, the baseline risk and number of cases was low and the confidence intervals were wide enough to have missed a clinically important effect of ICS on the risk of onset of diabetes. Second, we did not have biochemical validation of cases. Thus, case misclassification was possible, which would have diluted the results. Third, there was no follow-up. As ICS are recommended as maintenance therapy, future studies will be needed to evaluate the long term effects of ICS on these endpoints. The study only included patients on inhaled corticosteroids not the systemic one. Therefore, the study's results could not be generalized for all types of COPD patients. Moreover, the representative samples were not sufficient enough to represent the whole population. Further, it was a hospital based cross sectional study and researcher has done the study in a single place. So, it does not represent the whole population. Multi-centered longitudinal study may help in gaining wide knowledge to improve the knowledge about onset of diabetes in COPD patients on ICS. Finally, the patients included in this pooled analysis were, for the most part, free of any significant co-morbidity. In addition, for comparing of glycaemic control between two groups, it would have been better to conduct a pure analytical study; however, this study (comparative cross- sectional study design) is also useful for analysis of this comparison.

6. Conclusion and Recommendations

The relevance of development of type 2 diabetes mellitus in COPD patients obtained from recent studies may be a matter of debate. So further investigations are required. However, we should always consider clinical links with high dose ICS therapy in COPD patients. to scale back the likely risk of ICS induced diabetes at low or moderate doses the efficacy and pharmacokinetics of those drugs may have meticulous evaluation. So, ICS overuse has also to be addressed. additionally, improving the safety and efficacy of ICS therapy requires adequate patient selection and monitoring. Contemporary data may advocate upon taking care during administration of high dose ICS in development and evolution of diabetes. a far better therapeutic regimen to reduce the side effects can ensure quality management of COPD patients. Care providers and strategy makers need to ascertain satisfactory resource along with gaining ample information and efficiency in order that one cares and act on them. a serious portion of individuals are suffering from COPD in our country. This study showed the onset of diabetes is more in patients on ICS than in patients of bronchodilators. To reorganize their disease burden, community attentiveness about health care services and self-concern of COPD patients for his or her own health requirements are to be emphasized. Infrastructural development is required to supply appropriate referral service from grass root level for correct management of COPD patients. Confirming the acquiescence to medication and accurate lifestyle may be a significant issue for COPD patients. Service components' should be built up to proceed self-reporting of latest diabetic patients. The resource of health care system, knowledge, attitude and proficiency within the profession of care providers got to improve for attaining the specified outcome. The policy makers should be keen and cordial enough to uphold the mainstay of COPD management intimately with minimal or no burden of side effects

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