Plasma Glucose Levels of Asthma Patients Using Inhaled Fluticasone

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Research note

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Abstract

Objective: Inhaled fluticasone is used in asthma for a long duration. However, It's an adverse effect on glycaemia is debatable. This study explored the effect of inhaled fluticasone in long term asthma patients. A comparative cross-sectional study was conducted among the adult normoglycaemic asthma patients in Bangladesh between June 2017 to May 2018. The study groups were getting inhaled fluticasone for a minimum of three months whereas comparative group were not on any steroids. Each group had 35 eligible participants.

Results: In study group, mean plasma glucose at fasting was 5.27 ± 0.48 mmol/L, 2-hour after 75gm oral glucose was 6.04 ± 1.21 mmol/L and mean of HbA1c was 5.57 ± 0.41 % whereas in comparative group these were 5.17 ± 0.59 mmol/L, 5.69 ± 1.09 mmol/L, 5.47 ± 0.40 % respectively (p= 0.25, 0.20, 0.75 respectively). Duration of inhaled fluticasone use had no specific co-relation with fasting plasma glucose, plasma glucose 2-hour after 75gm oral glucose and HbA1c% (r= 0.016, p= 0.46; r= 0.015, p= 0.47; r= 0.019, p= 0.42 respectively).

Introduction

Asthma is a chronic inflammatory condition of respiratory tracts. It affects more than 300 million people worldwide, with a prediction of another additional 100 million people affected by 2025 [1]. Around 5.2% people of Bangladesh suffer from this disease with a death rate of 12.96/lac [2]. Most of these deaths can be avoided through timely and appropriate treatment. Medications used in asthma are classified as relievers and controller [3]. These are corticosteroids and leukotriene modifiers and bronchodilators. Inhaled corticosteroids (ICS) are commonly used for long term which is crucial for the management of persistent asthma which has clear adverse effect on multiple body system without any unifying consensus on glucose metabolism [4, 5]. Both prevalence and occurrence of type 2 diabetes are higher in patients with asthma [6]. Use of ICS in asthma for prolonged period and or higher dose has worsening effects on glycaemic status [7, 8, 9, 10]. Several studies were done on the adverse effects of ICS revealing inconsistent findings on glycaemic status of ICS users [11]. Therefore, this study was conducted on asthma patients to observe the glycaemic effect of inhaled fluticasone users in Dhaka, Bangladesh. Primary objective of the study was to determine the plasma glucose level on asthma patients on inhaled fluticasone. Plasma glucose level at fasting and 2 hours after 75 gm oral glucose intake between asthma patients on inhaled fluticasone and patients not having corticosteroids were compared as well.

Methods

A comparative cross sectional study was conducted on asthma patients attending outpatient Department of Internal Medicine and Respiratory Medicine of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between June 2017 to May2018. Ethical approval was taken from the institutional review board (IRB) of BSMMU. Asthma patients aged 18 years and above using inhaled fluticasone for at least three months were enrolled in study group. Asthma patients not using inhaled or

any other form of steroid were considered as the comparative group. Patients were enrolled using purposive sampling method. Both groups were on other asthma medications such as montelukast, theophylline and short acting or long acting bronchodilators. Patients with prior diagnosis or newly diagnosed as prediabetes and diabetes mellitus, receiver of oral or intra-articular or intranasal steroids or homeopathy or herbal remedies within last three months of enrolment, critically ill patients/ exacerbation, pregnancy or delivery within last 3 months were excluded from the study. Every participant was informed of the voluntary nature of participation and written informed consent was obtained. Only researcher had access to all personal data. In each group 35 patients were enrolled after exclusion of participants and there were total 70 participants. Seven patients were excluded from the study for abnormal plasma glucose level. Data were collected from comprehensive history, physical findings and laboratory reports. Fasting, 2-hour plasma glucose level after 75 g oral glucose intake and HbA1c% were measured in the department of Biochemistry, BSMMU using automated analyzer: Variant II, Architect Plus *ci*4100 manufactured by Abbott, Ilinois, USA. After 12 hours fasting at morning 2 ml of venous blood for fasting plasma glucose and 3 ml of blood for HbA1c% was collected using a 5 cc disposable syringe with full aseptic precaution. Second sample of blood was collected after 2 hours of oral intake of 75 gm dextrose for 2-hour plasma glucose level estimation. For plasma glucose blood sample was collected in glucose tube containing sodium fluoride/EDTA and for HbA1c% blood sample was collected in anticoagulated tube containing tri-potassium EDTA. To separate plasma for glucose level estimation blood sample was centrifuged for 15 minutes within 3 hours of sample collection. Then plasma samples were analyzed in automated machine. Blood samples for HbA1c% were directly analyzed in machine within 3 hours of collection. Diabetic and pre-diabetic patients were then excluded. Spirometry was done in the department of Physiology, BSMMU by HELIOS- 401 spirometer manufactured by RMS India. Statistical analysis was done using SPSS version 21.

Data were analyzed using SPSS version 19.0. Cross tabulation was conducted to differentiate the characteristics of study group and compare group. Independent sample t test was used to compare means of continuous data. A chi-square test or Fisher's exact test and analysis of variance (ANOVA) was conducted to observe the association between groups where applicable.

Operational Definition

Asthma patients- A patient was considered to have asthma when a competent and qualified physician diagnoses it on the basis of history, examination and relevant laboratory investigations.

Variability of limitation of expiratory airflow can be confirmed by documented airflow limitation: FEV1/FVC < 0.7 AND Bronchodilator (BD) reversibility test positive (increase in FEV1 > 12% & >200 mL from baseline [12].

Diabetes mellitus: Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or, 2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) or, HbA1c% ≥6.5%.

Impaired Glucose Tolerance (IGT): Fasting plasma glucose < 7.0 mmol/l (126 mg/dl) and 2-hour plasma glucose ≥ 7.8 mmol/l and < 11.1 mmol/l (140 mg/dl and 200 mg/dl).

Impaired Fasting Glucose (IFG): Fasting plasma glucose 6.1 to 6.9 mmol/l (110 mg/dl to 125 mg/dl) and 2-hour plasma glucose < 7.8 mmol/l (140 mg/dl) [13, 14]

Low, medium and high doses of inhaled fluticasone were 100–250 mcg/day, > 250–500 mcg/day, > 500 mcg/day respectively for dry powder inhaler (DPI) or hydroflouroalkane propellant (HFA) [12].

Results

Age range for study group was 18–55 years with a mean age of 35.51 ± 11.29 years and for comparative group it was 18–60 years with a mean age of 32.89 ± 11.23 years. Sex distribution in both groups was almost similar (48.6% and 51.4% male in study and comparative groups respectively). More than 88% of participants of both groups were non-smoker. The mean BMI (Kg/m^2) of study group was 24.85 ± 3.57 and comparative group was 23.13 ± 3.47 (Kg/m^2). Around 50% of participants of both groups had family history of asthma. Mean duration of asthma in study group was 9.04 ± 7.47 years ranging from 1 year to 32 years and for comparative group 6.90 ± 5.17 years 1.5 years to 20 years respectively. In both groups FEV1/FVC% was above 90% and FEV1 was above 84%. Cough was present in 100% of both groups. In study group shortness of breath, wheeze and chest tightness were other symptoms in 26 (74.3%), 26 (74.3%), 6 (17.1%) participants whereas in comparative group it was 29 (82.9%), 29 (82.9%), 9 (25.7%) respectively. Out of 35 participants in study group 18 (51.4%) were getting medium dose fluticasone, 15 (42.9%) were getting high dose fluticasone and rest were on low dose fluticasone. Fifteen (42.9%) participants of study group were getting inhaled fluticasone for 3 to 6 months, 9 (25.7%) for 6–12 months and rest were getting beyond 12 months (Table 1). The demographic and clinical characteristics have been described in Table 1. Table 2 and Table 3 explored the mean of fasting plasma glucose, 2-hour plasma glucose, HbA1c % and their comparison between the groups.

Table 1

Demographic and clinical characteristics of the study and comparative groups

Characteristics	Study Group (n = 35)	Comparative Group (n = 35)	P - value
Age - (year)	35.51 ± 11.29	32.89 ± 11.23	0.53
Sex – No. (%)	17(48.6)	18(51.4)	0.81
Male	17(51.4)	17(48.6)	
Female			
Smoking status – No. (%)	2(5.7)	2(5.7)	1.0
Smoker	2(5.7)	1(2.9)	
Ex-smoker	31(88.69)	32(91.4)	
Non-smoker			
Family history of asthma – No. (%)	17(48.6)	19(54.3)	0.63
Duration of asthma -(year)	9.04 ± 7.47	6.90 ± 5.17	0.19
Symptoms - No. (%)	35 (100)	35 (100)	-
Cough	26 (74.3)	29 (82.9)	0.32
Shortness of breath	26 (74.3)	29 (82.9)	0.38
Wheeze	6 (17.1)	9 (25.7)	0.38
Chest tightness			
BMI Kg/m^2	24.85 ± 3.57	23.13 ± 3.47	0.80
Lung function - %	95.59 ± 15.17	93.54 ± 14.82	0.51
FEV1/FVC	85.26 ± 24.52	84.49 ± 23.46	0.96
FEV1			
Fluticasone use – No. (%)	2 (5.7)	-	-
Dose	18 (51.4)		
Low dose	15 (42.9)		
Medium dose			
High dose			

Independent-Samples t-test was conducted for continuous variables

Chi-square test / Fisher's Exact test was conducted for categorical variables

Characteristics	Study Group (n = 35)	Comparative Group (n = 35)	P - value
Duration in months	15 (42.9)	-	-
< 6 months	9 (25.7)		
6–12 months	11 (31.4)		
> 12 months			
Independent-Samples t-test was conducted for continuous variables			
Chi-square test / Fisher's Exact test was conducted for categorical variables			

Table 2

Comparison of mean of fasting plasma glucose, 2-hour plasma glucose, HbA1c % between study and comparative groups

	Study Group (n = 35)	Comparative Group (n = 35)	P - value
Fasting plasma glucose (mmol/L)	5.27 ± 0.48	5.17 ± 0.59	0.25
2-hour plasma glucose (mmol/L)	6.04 ± 1.21	5.69 ± 1.09	0.20
HbA1c (%)	5.57 ± 0.41	5.47 ± 0.40	0.75
Independent-Samples t-test was conducted to compare between groups			

Table 3

Mean of fasting plasma glucose (FPG), 2-hour plasma glucose, HbA1c % of study group according to the dose of inhaled fluticasone (n = 35)

	Dose of IF	No. (%)	Mean ± SD	P - value
Fasting plasma glucose (mmol/L)	Low	2 (5.7)	5.35 ± 0.63	0.13
	Medium	18 (51.4)	5.42 ± 0.57	
	High	15 (42.9)	5.08 ± 0.28	
2-hour plasma glucose (mmol/L)	Low	2 (5.7)	4.8 ± 0.42	0.31
	Medium	18 (51.4)	6.02 ± 1.24	
	High	15 (42.9)	6.22 ± 1.20	
HbA1c (%)	Low	2 (5.7)	5.70 ± 0.28	0.81
	Medium	18 (51.4)	5.53 ± 0.34	
	High	15 (42.9)	5.56 ± 0.52	
IF- inhaled fluticasone				
Comparison within groups was conducted using analysis of variance (ANOVA)				

The mean fasting plasma glucose, 2-hour PG and HbA1c of study group are higher than that of the comparative group but not statistically significant (Table II, p = 0.25, 0.20, 0.75 respectively). There were no significant differences of values fasting plasma glucose, 2-hour plasma glucose, HbA1c (%) in terms of low, medium and dose inhaled fluticasone use in study group (Table III). There was no specific correlation of duration of fluticasone use with values of fasting plasma glucose, 2-hour plasma glucose, HbA1c% of respondents of study group (n = 35) (Supplementary file- Fig: 1A, 1B, 1C).

Discussions

This comparative cross sectional study was conducted to observe the effects of inhaled fluticasone on plasma glucose levels of asthma patients. Study group involved 35 physician diagnosed asthma patients using inhaled fluticasone for at least 3 months and comparative group involved 35 physician diagnosed asthma patients not using any form of steroids for at least 3 months before the enrolment. Both groups were taking other asthma medications apart from ICS as per criteria mentioned. There was no significant difference of age, sex, smoking status, family history, duration of asthma, asthma symptoms, BMI, lung function on spirometry among the participants between the groups (Table I). In the current study it was found that mean fasting plasma glucose, mean 2-hour plasma glucose after 75 gm oral glucose intake, mean HbA1c% of study group do not have statistically significant difference from that of the comparative group (P = 0.25, 0.20, 0.75 respectively). Findings of current study is supported by large retrospective double blind placebo control trial and also several other studies [15, 16, 17, 18, 19, 20]. It is inconsistent

finding in a prospective study [7, 8, 10]. One possible explanation of these finding could be genetic predisposition of individual to insulin resistance which could lead to worsening glycaemic status.

Duration of use of inhaled fluticasone had no specific correlation with fasting plasma glucose, 2-hour PG, HbA1c values that is supported by other study [8].

Yucel et al. found no effect of dose of inhaled corticosteroid and HbA1c value likewise in the current study there were no significant effects of dose of inhaled fluticasone use on fasting plasma glucose, 2-hour plasma glucose after 75 gm oral glucose and HbA1c% in the study group [8]. Some studies found dose dependent alteration of plasma glucose level although the subjects were diabetic [5, 11, 21].

Conclusions

Use of inhaled fluticasone for 3months or more had no significant effect on plasma glucose of asthma patients. Duration of use of inhaled fluticasone had no specific correlation with blood sugar and HbA1c values. Inhaled fluticasone had no significant effect on glycaemic status. So it appears using inhaled fluticasone in asthma for prolonged duration is safe on glycaemic aspect. However, larger randomized controlled trials are required to draw further conclusion.

Limitations

The study was conducted with an effort to minimize the limitations still there were some: study was not multi-centered which could represent different populations, sampling method was purposive that might have led to bias, compliance of patients to inhaled fluticasone might not be good beyond query, apart from glycaemic effect other systemic effects of inhaled corticosteroids were not addressed.

Abbreviations

BD - Bronchodilator

BSMMU - Bangabandhu Sheikh Mujib Medical University

HFA - Hydroflouroalkane propellant

ICS - Inhaled corticosteroids

IFG - Impaired Fasting Glucose

IGT - Impaired Glucose Tolerance

IRB - institutional review board

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (Approval number- BSMMU/2017/6575). Purpose, benefit and risk of the study were explained to each participant in order to obtain written consent from study participants prior to data collection.

Consent to publish

Authors provide consent to publish. Participants were informed regarding publication during taking consent.

Availability of data and materials

All the data and materials are available upon request.

Competing interests

Authors declare no competing interest.

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Authors' contributions

Md. Atikur Rahman conceptualized the study, collected data, analyzed, interpreted findings and drafted the manuscript. K M Saif-Ur-Rahman critically reviewed the manuscript and made necessary modifications. All other authors had contribution in sample collection, data screening, analysis and writing manuscript. All authors have gone through and agreed to the final manuscript.

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Figures

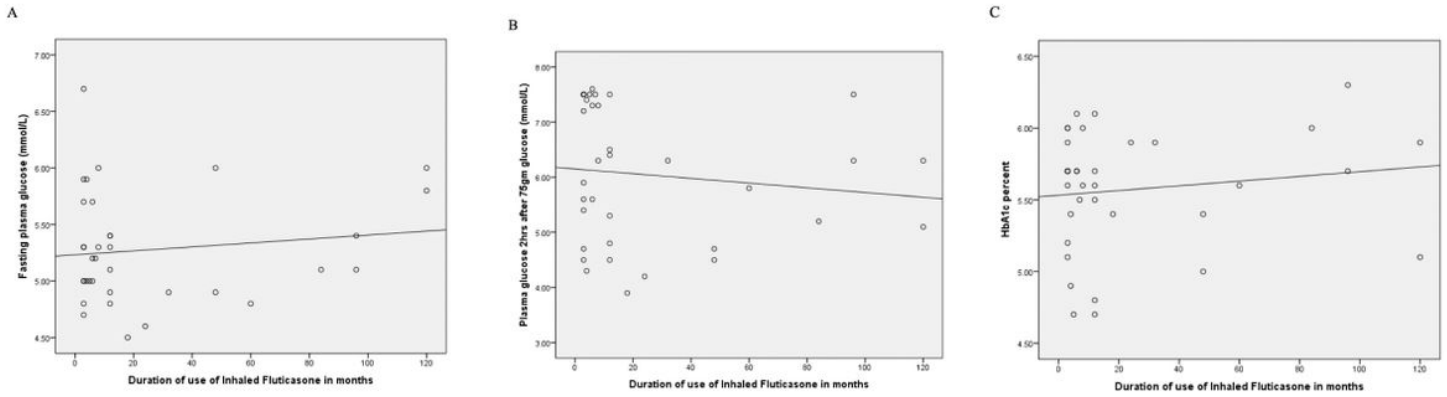

Figure 1

A: Duration of fluticasone use and fasting plasma glucose values of respondents of the study group (n=35) had no specific correlation (r= 0.016, p= 0.46). B: Duration of fluticasone use and 2-hour plasma glucose values of respondents of the study group (n=35) had no specific correlation (r= 0.015, p= 0.47). C: Duration of fluticasone use and HbA1c% values of respondents of the study group (n=35) had no specific correlation (r= 0.019, p= 0.42).