Original article:

Diabetic and non-diabetic subjects with asthma

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Abstract:

Introduction: This study is undertaken to find out whether high dose inhaled steroid therapy cause derangement of blood glucose and serum lipid profile in diabetic and non-diabetic patients with asthma.

Methodology: Total, 80 cases were selected. The patients were divided into 2 groups. Group 1- comprising of 20 patients who were diagnosed cases of asthma and diabetes mellitus. Patients of both group 1&2 were then prescribed high dose inhaled steroids (1600µ gm/day of Budesonide or 1000µgm/day of Fluticasone) for 4 weeks through meter dose inhaler with spacer. Four weeks after initiation of high dose inhaled steroids the patients were reassessed for improvement or deterioration by clinical signs like respiratory rate, presence of rhonchi, blood pressure. FEV1, fasting and post prandial blood glucose, fasting serum lipid profile (including total cholesterol, HDL cholesterol ,LDL cholesterol, VLDL cholesterol, triglyceride) to detect any change in these parameters from their previous values.

Results: Statistically significant improvement in the FEV1 in both groups following inhaled steroid therapy. No statistically significant difference in the post prandial blood glucose levels before and after high dose inhaled steroid therapy in all the groups. No significant difference in the levels of fasting, post prandial blood glucose in the diabetic, non-diabetic patients or in those patients with impaired fasting glucose. No significant difference in the levels of fasting, or post prandial blood glucose in group 1 and 2 patients before and after receiving budesonide or fluticasone.

Conclusion: Following 4 weeks of high dose inhaled steroid therapy both groups of patients showed improved asthma control and significant improvement in FEV1. No significant change in the blood glucose and fasting lipid profile in both groups of patients. Even those patients who had impaired fasting glucose did not show any significant change in the blood glucose levels after 4 weeks of inhaled steroid therapy.

Keywords: Asthma, High dose inhaled steroid, diabetes, blood glucose, lipid profile.

Introduction:

Asthma is one of the diseases longest recognized as a distinct entity(1).From the ages of the Pharaonic Egypt indirect evidence concerning asthma can be obtained from the papyrus Ebers (1550 B.C.). In Greek “asthma” means to exhale with open mouth that is to pant .The writings of the Hippocratic School recognized the seasonal and paroxysmal nature of asthmatic attacks (2).

In the recent times asthma has increased dramatically in prevalence and is now recognized as a major cause of disability, medical expense and preventable death (3). Asthma is a worldwide problem with an estimated 300 million affected individuals .Global prevalence of asthma varies from 1% to 18% in different countries. WHO estimated 15 million disability adjusted life years (DALY) are lost annually due to asthma. Annual mortality due to asthma is estimated to be 2, 50,000 worldwide (4).

Asthma is a chronic inflammatory disorder of airways in which many cells and cellular elements play a role. The chronic inflammation is associated

with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or early morning. These episodes are usually associated with widespread but variable, airway obstruction within the lung that is often reversible either spontaneously or with therapy (5).

Asthma is a disease of misdirected immunity with the direction of immune function being influenced by many genes and probably also by airway infections especially with viruses, but established in the first few years of life. Combined use of anti-inflammatory and bronchodilator therapies coupled with measures to reduce environmental exposures is the currently available modalities for asthma therapy (6,7). The most effective and commonly used controller therapy for asthma is an inhaled corticosteroid which inhibits the production of pro- inflammatory cytokines and reduces bronchial reactivity and frequency of exacerbations. Oral and parenteral corticosteroids are effective but are notorious for their side effects. Several systemic side effects of inhaled steroids have been described like adrenal insufficiency, growth suppression in children, osteoporosis, bruising, metabolic abnormalities and psychiatric disturbances(8).

There has been a worldwide expansion of type 2 diabetes mellitus. Thus we can well imagine that there quite a number of patients who suffer from both diabetes and asthma. When these patients are prescribed steroid inhalers especially in high doses there is some apprehension among the treating physicians regarding the metabolic side effects of these drugs? As we know the oral steroids even when taken for short period can cause hyperglycemia but whether inhaled steroids carry similar risk has not been extensively investigated. So this study is undertaken to find out whether high dose inhaled steroid therapy cause derangement of blood glucose and serum lipid profile in diabetic and non-diabetic patients with asthma.

Methodology:

Total, 80 cases were selected. These patients were previously diagnosed as cases of, moderate to severe persistent asthma as per GINA guidelines. The patients were divided into 2 groups. Group 1- comprising of 20 patients who were diagnosed cases of asthma and diabetes mellitus. Most of the patients had type 2 diabetes and only a few patients were suffering from type 1 diabetes. All the patients had satisfactory glycemic control (by diet modification, oral glucose lowering agent or insulin) at the time of initiation of the study, as evident their fasting, post prandial blood sugars and glycated hemoglobin levels and Group 2 comprising of 60 patients who were diagnosed cases of asthma and did not have diabetes mellitus. A few patients of impaired fasting glucose were also included in this group. Impaired fasting glucose is defined as fasting plasma glucose 100 mg/dl-125mg/dl.

Exclusion criteria included uncontrolled diabetes mellitus, patients on other drugs that alter blood glucose and lipids like thiazide diuretics, statins, and fibrates, systemic steroid therapy within 6 weeks before initiation of the study, uncontrolled infection, liver disease and renal failure, recent acute exacerbation requiring hospitalization within 6 weeks before initiation of the study and sputum positive pulmonary tuberculosis.

Duration of follow up is 4 weeks. Physical examination including general survey and respiratory system examination was done and different parameters like blood pressure, respiratory rate, and presence of rhonchi were noted. Spirometry was done

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and FEV1 of each patient was noted. Other laboratory investigations done at the initiation of the study involved are hemoglobin, total leucocyte count, fasting blood glucose, post prandial blood glucose, urea, creatinine, fasting serum lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglyceride, HbA1Cfor the diabetic patients, Chest X-ray.

Patients of both group 1&2 were then prescribed high dose inhaled steroids (1600µ gm/day of Budesonide or 1000µgm/day of Fluticasone) for 4 weeks through meter dose inhaler with spacer. Detailed instruction regarding use of MDI and spacer was explained to each patient. All patients were on additional long acting β 2 agonist salmeterol MDI which they were already taking at the time of initiation of the study. Patients suffering from diabetes were asked to continue with their diet, and anti-diabetic medication (oral glucose lowering agent or insulin) on which their blood glucose was controlled prior to the initiation of the study. No modification of diet or anti-diabetic medication was done after the patients were enrolled for the study. Four weeks after the initiation of the high dose inhaled steroids the patients were reassessed for improvement or deterioration by clinical signs like respiratory rate, presence of rhonchi, blood pressure. FEV1, fasting and post prandial blood glucose, fasting serum lipid profile (including total cholesterol, HDL cholesterol ,LDL cholesterol, VLDL cholesterol, triglyceride) to detect any change in these parameters from their previous values.

Results:

The group 1 patients had mean FEV1 of 74.4% before inhaled steroid therapy and 78.1% after inhaled steroid therapy. The group 2 patients had mean FEV1 74.2% before inhaled steroid therapy and 78.36% after inhaled steroid therapy. This improvement in the FEV1 in both groups following inhaled steroid therapy was statistically significant ($p<0.001$ in both groups). It was seen that in group 1 presence of rhonchi decreased from 70% to 35% after administration of inhaled steroid for one month. In group 2 presence of rhonchi decreased from 57% to 30%. So, inhaled steroid therapy was seen to be highly efficacious in both groups. (Figure 1).

In the group 1 patients the mean respiratory rate before and after the initiation of steroid therapy was 15.65/min and 14.4/min respectively ($p=0.003$). The respiratory before and after high dose inhaled steroid therapy in the group 2 patients was 15.58/min and 14.68/min respectively ($p<0.001$). In both groups the respiratory rate after high dose steroid therapy was less than that before therapy and statistically this change was significant. The mean systolic blood pressure before and after high dose inhaled steroid therapy in group 1 was 128mmof Hg and 126mm of Hg ($p=0.1$) the mean systolic blood pressure before and after high dose inhaled steroid therapy in group2 was 128 mm of Hg and 127.7mm of Hg respectively ($p=0.57$). The mean diastolic blood pressure before and after high dose inhaled steroid therapy in group 1 was 80.6 mm of Hg and 82 mm of Hg respectively($p=0.4$). The mean diastolic blood pressure before and after high dose inhaled steroid therapy in group2 was 77.96mm of Hg and 78.71 mm of Hg respectively ($p=0.3$). Thus there was no statistically significant difference in the systolic or diastolic blood pressures before and after inhaled steroid therapy, in all the groups. The mean fasting blood glucose before and after high dose inhaled steroid therapy in group 1 patients was 107.5mg/dl and 107.6mg/dl respectively ($p=0.96$). The mean fasting blood glucose before and after high dose

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inhaled steroid therapy in group2 patients was 85.48 and 85.1 respectively (p=0.78). The mean post prandial blood glucose before and after high dose inhaled steroid therapy in group 1 patients was 138.3mg/dl and 143.1mg/dl respectively (p=0.2). The mean post prandial blood glucose before and after high dose inhaled steroid therapy in group 2patients was 114.5mg/dl and 114.3mg/dl respectively (p=0.87). Thus there was no statistically significant difference in the fasting blood glucose levels before and after high dose inhaled steroid therapy in all the groups. The mean total cholesterol levels before and after inhaled steroid therapy in group 1 patients was 188.76mg/dl and 188.61mg/dl respectively (p=0.92). (Table 1)

The mean total cholesterol levels before and after inhaled steroid therapy in group2 patients was 172.47mg/dl and 171.17mg/dl respectively (p=0.31). The mean high density cholesterol levels before and after inhaled steroid therapy in group 1 patients was 39.5mg/dl and 41.35mg/dl respectively (p=0.09). The mean high density cholesterol levels before and after inhaled steroid therapy in group2 patients was 45.55mg/dl and45.11mg/dl respectively (p=0.47). The mean low density cholesterol levels before and after inhaled steroid therapy in group 1 patients was 114.85mg/dl and 113.30mg/dl respectively (p=0.4). The mean low density cholesterol levels before and after inhaled steroid therapy in group2 patients was 98.06mg/dl and 97.85mg/dl respectively (p=0.82). The mean very low density cholesterol levels before and after inhaled steroid therapy in group 1 patients was34.39mg/dl and 33.96mg/dl respectively (p=0.52). The mean very low density cholesterol levels before and after inhaled steroid therapy in group2 patients was 28.86mg/dl and 28.21mg/dl respectively (p=0.16). The mean TG levels before and after inhaled steroid therapy in group 1 patients was 172mg/dl and 169.8mg/dl respectively (p=0.52). The mean TG levels before and after inhaled steroid therapy in group 2 patients was144.30mg/dl and 141.05mg/dl respectively (p=0.16). Thus no significant difference was found in the levels of TC, HDLC, LDLC, VLDLC, TG, before and after high dose of inhaled steroid therapy in both the diabetic and non-diabetic patients. The mean fasting blood glucose before and after high dose inhaled steroid therapy in 5 patients with impaired fasting glucose was 106.2 mg/dl and 96.6 mg/dl respectively (p=0.2). The mean post prandial blood glucose before and after high dose inhaled steroid therapy in 5 patients with impaired fasting glucose was146.2mg/dl and 136mg/dl (p=0.21). Thus there was no statistically significant difference in the fasting and post prandial blood glucose levels before and after high dose inhaled steroid therapy.(Table 1) Oral candidiasis was found in 10% of the group 1 patients and 5% of the group 2 patients. Review of literature showed that clinical infection was observed in about 5% of cases (160-164). Only 1 patient belonging to group 2 developed dysphonia.

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Table 1: Comparison of different parameters among groups before and after 4 weeks of high dose inhaled steroid therapy

		Mean	N	Std. Deviation	Std. Error Mean	T value	P value
Pair 1	RR_1	15.6500	20	1.7852	.3992	3.387	.003
	RR_2	14.4000	20	1.4654	.3277		
Pair 2	SBP_1	128.0000	20	13.0263	2.9128	1.690	.107
	SBP_2	126.4000	20	12.1152	2.7090		
Pair 3	DBP_1	80.6000	20	8.8758	1.9847	-.815	.425
	DBP_2	82.0000	20	8.4853	1.8974		
Pair 4	FBG_1	107.5000	20	13.0888	2.9267	-.048	.962
	FBG_2	107.6000	20	11.9137	2.6640		
Pair 5	PPBG_1	138.3000	20	21.8153	4.8780	-1.312	.205
	PPBG_2	143.1000	20	21.5380	4.8160		
Pair 6	TC_1	188.7900	20	35.5088	7.9400	.092	.927
	TC_2	188.6100	20	35.5081	7.9399		
Pair 7	HDL_1	39.5500	20	6.5331	1.4608	-1.783	.091
	HDL_2	41.3500	20	6.8309	1.5274		
Pair 8	LDL_1	114.8500	20	28.0569	6.2737	.860	.401
	LDL_2	113.3000	20	28.4014	6.3508		
Pair 9	VLDL_1	34.3900	20	13.8923	3.1064	.645	.527
	VLDL_2	33.9600	20	13.7100	3.0657		
Pair 10	TG_1	171.9500	20	69.4614	15.5321	.645	.527
	TG_2	169.8000	20	68.5501	15.3283		
Pair 11	FEV1_1	74.4000	20	3.8030	.8504	-7.431	<.001
	FEV1_2	78.1000	20	4.02	.9000		

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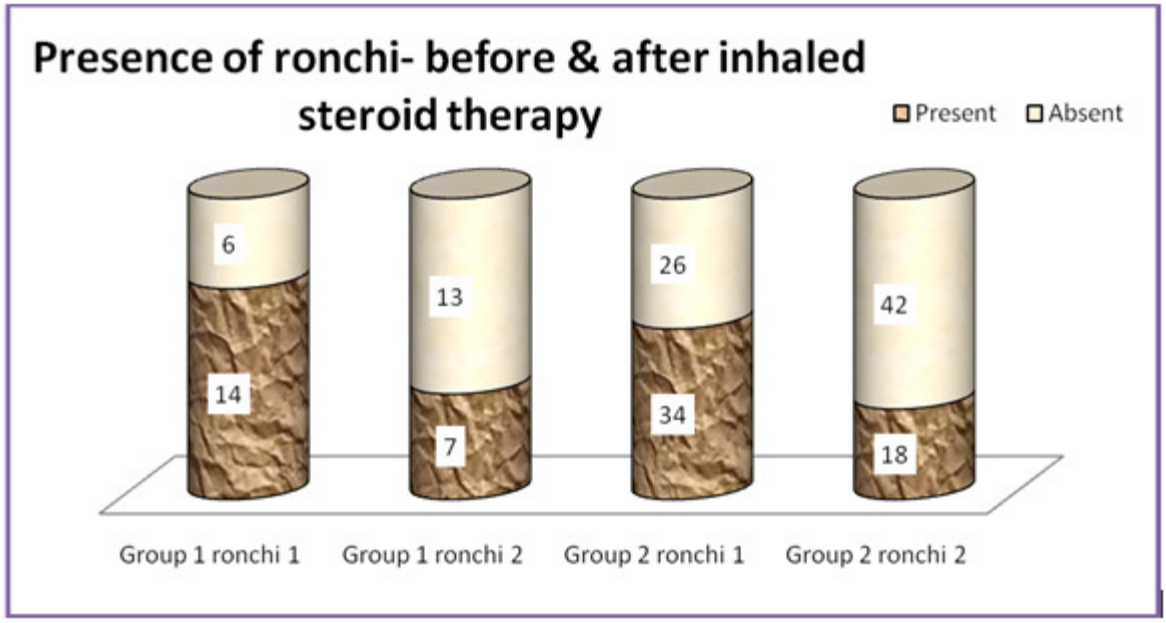
Figure 1: Presence of Rhonchi before and after Inhaled Steroid Therapy



Discussion:

We found no statistically significant difference in the post prandial blood glucose levels before and after high dose inhaled steroid therapy in all the groups. NandiniDendukuri, et al, reported a nested case-control designed study on the association between current use of inhaled corticosteroids and the risk of using antidiabetic medications among a cohort of 21,645 elderly subjects.They also did not observe a statistically significant increase in risk among users of high-dose beclomethasone compared to nonusers, after adjusting for covariates. They concluded that their results did not indicate an increased risk of diabetes among current users of inhaled corticosteroids (9). J L Faul, W Tormey, V Tormey, C Burke. Reported a case of 67yrs man suffering from T2dm and asthma for 10 years .His glycemic control worsened as evident from his HbA1Cvalues following initiation of high dose inhaled steroid therapy fluticasone propionate 2000 µg per day by metered dose inhaler through a Volumatic spacer device after 3 weeks and he developed glycosuria which improved on reducing the dose of Fluticasone (10). In a another study form UK by Ebden .P. et al, the effect of high dose of inhaled beclomethasonedipropionate (2000 µ gm/ day for 2 weeks) on glucose tolerance tests, insulin levels, fasting cholesterol & triglyceride concentrations in 14 normal & 10 elderly diet controlled diabetic patients, in a single blind placebo controlled trial found no significant difference in glucose or lipid metabolism in either group (2). Dendukuri M et al, from Finland conducted a longitudinal study of the anti-asthmatic & metabolic effects of inhaled Budesonide in initially high (800 µ gm/ m2/ day for 1 month) and subsequently lower (400 µ gm/m2/ day for 4 months) in children with asthma aged 5 to 10 years. The treatment had no significant effect on BMI or glucose tolerance. However the high dosage increased significantly the ratio of serum insulin to blood glucose, calculated from the areas under the incremental 2 hour curves in the GTT (medians- 17.3

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vs. 23.2 mU /mmol). After lowering the dosage, the ratio declined significantly to 13.5mU/mmol (P= 0.0164). Kruszynska et al observed the metabolic effects of 4 weeks of high dose inhaled beclomethasone dipropionate (500 µgms BD) in 9 normal subjects. No effect was found on fasting blood glucose concentration or glycated hemoglobin concentration. Peak blood glucose concentrations 30 minutes after a 75 gm oral glucose load was, however, significantly higher. After treatment there was 36% increase in fasting serum insulin conc. and 32% increase in the area under the serum insulin conc. curve after glucose challenge (12). Kiviranta K, et al studied the effect of inhaled high dose steroids on 15 adults with unstable asthma & 15 healthy controls for 8 months. The study concluded that in patients stressed by uncontrolled asthma, the anti-asthmatic effect of high dose beclomethasone dipropionate& Budesonide was accompanied by a significant initial decrease in insulin resistance with a parallel improvement in glucose tolerance. During the prolonged treatment a small increase in insulin sensitivity was found. The overall effect of beclomethasone& Budesonide inhalations on carbohydrate metabolisms maybe beneficial in patients with uncontrolled asthma (12). In our study, no significant difference was found in the levels of TC, HDLC, LDLC, VLDLC, TG, before and after high dose of inhaled steroid therapy in both the diabetic and non-diabetic patients. Yabuz O, et al found no significant change of TG concentrations before & after Budesonide therapy However, serum fasting CH decreased slightly & HDL-C concentrations increased (13). This finding is similar to that observed by Yavuz.p.et al (14), and contrary to the findings of Passalacqua M, who found significantly increased serum HDL cholesterol after the high dosage budesonide.(14)Kivaranta et al. found High dose inhaled beclomethasone dipropionate treatment raised the fasting plasma CH conc. and HDL-C (12).

We also did not find any significant difference in the levels of fasting, post prandial blood glucose in the diabetic, non-diabetic patients or in those patients with impaired fasting glucose. There was no significant difference in the levels of fasting, or post prandial blood glucose in group 1 and 2 patients before and after receiving budesonide or fluticasone. This finding corroborates with the findings of NandiniDendukuri,et al , Ebden .P. et al, Turpeinen M et al, Kruszynska et al. however we did not measure the serum insulin concentration.

Conclusion:

This before and after comparative study was done with 2 groups of patients.Group 1 – consisting of 20 patients who were suffering from both diabetes mellitus & asthma. This group comprised of patients of both type 1 diabetes (n=4) and type 2 diabetes (n=16). Group 2 comprised of 60 non-diabetic patients with asthma. This group contained 5 patients who had impaired fasting glucose. Following 4 weeks of high dose inhaled steroid therapy, both groups of patients showed improved asthma control and significant improvement in FEV1. There was no significant change in the blood glucose and fasting lipid profile in both groups of patients. Even those patients who had impaired fasting glucose did not show any significant change in the blood glucose levels after 4 weeks of inhaled steroid therapy.

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