EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 1
174-177
Year: 2016

EFFECT OF INHALED CORTICOSTEROIDS ON GLUCOLIPOTOXICITY AND HIGH SENSITIVITY C-REACTIVE PROTEIN IN ASTHMA PATIENTS

Dr. R. Reeta[1*], Dr. Kulkarni Sweta[2], S. Krupashree[3], Dr. R. Pajanivel[4], Dr Ramesh. R

[1,2]Assistant Professor, Department of Biochemistry Mahatma Gandhi Medical College and Research Institute Puducherry – 607402 India.
[3]Second Year MBBS Student, Mahatma Gandhi Medical College and Research Institute Puducherry – 607402.
[4]Professor, Department of Pulmonary Medicine Mahatma Gandhi Medical College and Research Institute Puducherry – 607402.
[5]Professor, Department of Biochemistry Mahatma Gandhi Medical College and Research Institute Puducherry – 607402.

***Author for Correspondence: Dr. R. Reeta**
Assistant Professor, Department of Biochemistry Mahatma Gandhi Medical College and Research Institute Puducherry – 607402 India.

Article Received on 23/10/2015 **Article Revised on 13/11/2015** **Article Accepted on 3/12/2015**

ABSTRACT

Background: Asthma is a chronic inflammatory disease which is treated using inhaled corticosteroids. Certain studies suggest that use of inhaled steroids may lead to a decrease in the levels of hsCRP. It has also been suggested that CRP might be used as a marker for systemic inflammation in case of asthma patients. On the other hand, it has also been seen that use of inhaled corticosteroids may increase the risk of developing diabetes mellitus and atherosclerosis. This study aims to evaluate and correlate the hsCRP, blood glucose, lipid profile and glycated albumin with the pulmonary function tests in patients undergoing short term inhaled corticosteroid therapy. **Materials and Methods:** The study was conducted on 30 patients attending the outpatient department in pulmonary medicine. Blood glucose, lipid profile, hsCRP and glycated albumin were measured in the patients, once before the start of treatment and once after six weeks.. The values were compared. A correlation analysis test was performed to see the relation of blood glucose, lipid profile and pulmonary function test with hsCRP and glycated albumin. Biochemical tests were done using IFCC approved methods. **Results:** This study documents increased levels of blood glucose, TAG and VLDL in asthma patients after treatment with ICS for one month. It also establishes a positive relation of ICS with pulmonary function. **Conclusions:** In our study, we have found significant changes in blood glucose, TAG and VLDL in patients who underwent inhaled corticosteroid therapy for a month. We were also able to record a significant improvement in the pulmonary function tests of these patients after treatment with ICS.

KEYWORDS: Lipid profile, hsCRP, Inhaled corticosteroids, Glycated albumin, Glucolipotoxicity.

INTRODUCTION

Asthma is one of the most prevalent diseases affecting people worldwide. It is a chronic respiratory disease characterized by increased airway inflammation, airway hyperactivity and airflow obstruction in response to specific triggers. It is commonly treated with two classes of medications: inhaled corticosteroids, used as a daily control medication and β-adrenergic agonists, used to induce bronchodilation.[1]

The existence of systemic inflammation in asthma is supported by increased levels of serum fibrinogen and amyloid A, also a positive relationship with the serum acute phase reactant has been reported.[2,3]

Numerous studies indicate that serum high sensitivity C-reactive protein (hsCRP) levels may be suitable for the detection of systemic inflammation in asthma and increased levels are associated with decreased pulmonary function, which suggests that hsCRP could be adjuvant systemic marker that reflects the degree of local airway inflammation.[4,5] Studies demonstrate that use of corticosteroids decrease the inflammation and the levels of CRP.[6,7]

Glucocorticoids have been used for several years in a variety of diseases as potent anti-inflammatory and immunosuppressive agents. It has been generally perceived that exogenous glucocorticoids inhaled as well as oral, adversely affect the metabolism. The metabolic effects comprise elevated serum glucose concentration

and hyperlipidaemia, both are closely linked to the "Metabolic Syndrome" with an increased risk for type II diabetes, cardiovascular disease and stroke.[8] Such glucocorticoid-induced effects are mediated by binding to receptors in the liver and in muscle as well as adipose tissue and partly may be due to reduced insulin sensitivity.[9]

The effects of inhaled glucocorticoids (ICS), regularly used for many years in the treatment of asthma have been studied in adults and they are conflicting.[10,11]

The present study was planned to assess the effects of short-term treatment of inhaled glucocorticoid treatment on hsCRP, glycated albumin and lipid profile in adults with asthma, average serum glucose concentration during the preceding 2-3 weeks can be assessed by glycated albumin.

METHODOLOGY

This was a prospective study which was undertaken in thirty adults newly diagnosed with asthma attending the outpatient department of pulmonary medicine in a tertiary care hospital in Pondicherry. The study was carried out after obtaining a clearance from Institute human ethical committee and informed consent from each study subjects in their local language.

Inclusion criteria: patients diagnosed with asthma and not treated with any asthma therapy, short acting bronchodilators (SABA) and long acting bronchodilators (LABA), antihistamine, prior to inclusion into the study, with normal lipid profile and blood glucose levels.

Exclusion criteria: patients with dyslipidemia, comorbid conditions like diabetes mellitus, obesity ($BMI>30kg.m^2$), smoking, hepatic and renal disorders. Patients with Pulmonary diseases (like COPD, parenchymal lung disease and Bronchiectasis) were excluded, since all the above mentioned conditions may alter the biochemical parameters.

Five ml of venous blood was collected from the subjects after obtaining informed consent. Blood sample was collected twice, once before initiation of therapy and the second, after six weeks of ICS therapy. The sample was used to analyse hsCRP, fasting Plasma glucose, Glycated albumin and Lipid profile (Triacylglycerol, Total cholesterol, HDL cholesterol and LDL cholesterol was compacted by Friedwald equation, LDL cholesterol = total cholesterol-(HDL cholesterol +VLDL) where VLDL= TAG/5.

Bio-chemical parameters were estimated based on established methods approved by the IFCC. All assays were carried out on fully automated chemistry analyser. Pulmonary function test was performed using a portable MIR winspirobank II spirometer.

STATISTICAL ANALYSIS

All the data were expressed as mean+/- SD. Paired't' test and a Pearson's correlation analysis were used. A p value <0.05 has been considered as statistically significant for all statistical tests. SPSS version 20 was used for all statistical analysis.

RESULTS

All physiological and biochemical parameters were expressed as mean ± SD; results were compared using a paired't' test. Table 1, represents the mean, SD and p values of blood glucose, hsCRP, FEV_1, FVC and FEV_1/FVC both before and after ICS treatment for six weeks. A p -value less than 0.05 was considered to be significant.

Table 2, represents the mean, SD and p values of cholesterol, TAG, HDL, LDL and VLDL. A p- value less than 0.05 was considered significant.

Table 3 represents the correlation of the pulmonary function test with hsCRP and glycated albumin. A correlation coefficient greater than 0.5 was considered to be having a significant correlation.

In the present study, there was a significant difference in the blood glucose, pulmonary function test, TAG and VLDL levels after the use of ICS. There was no statistically significant difference in other parameters. No significant correlation was found between hsCRP and Glycated albumin with the FEV_1 and FVC (table 3).

TABLE 1-Comparison of Fasting Blood Glucose, glycated albumin, CRP, FEV_1, FVC and FEV_1/FVC before and after ICS.

Parameters	Before ICS (N=30)		After ICS (N=30)		p-value
	mean	SD	mean	SD	
FBG(mg/dl)	97.13	20.089	109.4	20.992	0.03*
Gly Albumin%	0.3	0.2	0.4	0.1	0.001*
hsCRP(mg/L)	2.92	5.9	2.68	2.17	0.84
FEV1%	72.13	16.87	77.4	12.436	0.001*
FVC%	82.97	16.874	86.73	13.266	0.58
FEV1/FVC%	87.26	12.544	100.706	18.098	0.1

FBG- Fasting Blood Glucose.
Gly- Glycated.
hsCRP- High Sensitivity C-reactive Protein.
FEV_1- Forced Expiratory Volume in first second.
FVC-Forced Vital Capacity.
*indicates p-value less than 0.05.

TABLE 2- Comparison of lipid profile before and after ICS.

Parameters	Before ICS (N=30)		After ICS (N=30)		p- value
	Mean	SD	Mean	SD	
Cholesterol(mg/dl)	185.56	23.447	191.54	35.609	0.336
TAG(mg/dl)	126.97	33.191	180.97	88.762	0.002*
HDL(mg/dl)	42.63	8.5	40.77	7.396	0.363
LDL(mg/dl)	117.93	19.61	113.14	31.224	0.45
VLDL(mg/dl)	27.25	9.05	35.79	17.799	0.014*

TAG- Tri Acyl Glycerol.
HDL-High Density Lipoprotein.
LDL-Low Density Lipoprotein.
VLDL- Very Low Density Lipoprotein.
*indicates p-value less than 0.05.

TABLE 3- Correlation of pulmonary function with hsCRP and glycated albumin.

Parameters (N=60)	'r' value	'p' value
FEV1% & hsCRP	0.2	0.06
FEV1% & Gly Albumin	0.024	0.59
FVC% & hsCRP	0.094	0.125
FVC% & Gly Albumin	0.13	0.855
FEV1/FVC %(Ratio) & hsCRP	0.105	0.47
FEV1/FVC %(Ratio) & Gly Albumin	0.024	0.321

Gly- Glycated.
hsCRP- High Sensitivity C-reactive Protein.
FEV_1- Forced Expiratory Volume in first second.
FVC-Forced Vital Capacity.

DISCUSSION

Asthma is a chronic inflammatory disease of the airways. Inflammation of the walls of the bronchus results in difficulty in breathing and hence panting is seen. Treatment generally involves use of inhaled corticosteroids, used as a daily control medication and β-adrenergic agonists, used to induce bronchodilation.[1]

During inflammatory response, there is an increase in levels of Amyloid A and serum fibrinogen.[2,3] Along with this an increase in levels of CRP is also seen.[6,7] The mechanism of action of these medications is a two way process- firstly, they reduce the local inflammation and secondly they also cause bronchodilation, thus relieving the symptoms of asthma. As these corticosteroids reduce the local inflammation, a decrease in levels of hsCRP is seen.[6,7] However, in our study the decrease in levels of hsCRP was not statistically significant. This could have been as a result of other factors which may have caused systemic inflammation leading to a rise in hsCRP levels.

An increase in levels of glycated albumin is observed. Glycated albumin is a measure of the average serum glucose concentration in the preceding 2-3 weeks. So an increase in its value further confirms the increase in levels of blood glucose. This reaffirms that an increase in glycated albumin is seen during active treatment with glucocorticoids.[12] However in our study, the levels of glycated albumin both before and after ICS treatment were within the reference range. Hence, it can't be used as an index of glycemic status for short term use of ICS.
In the present study a significant increase in blood glucose has been observed. This may be because of the metabolic effect of ICS which causes an increase in insulin resistance and other mechanisms affecting the pancreatic β-cells such as decrease in insulin production increase in insulin resistance, reduction in insulin sensitivity or due to increase in hepatic gluconeogenesis. A reduction in transport of glucose along with an increase in cycling of glucose is seen.[13]

This is because of increase in activity of glucose-6-phosphatase. As a result insulin secretion is decreased. Hence, an increase in serum glucose levels is observed.[14] Hence, patients undergoing ICS treatment are at a risk of developing Metabolic syndrome and development of Diabetes Mellitus, though the risk isn't high enough to avoid treatment.[15] The increase in levels of VLDL and TAG are due to increased stimulation of hormone sensitive lipase by the corticosteroids and may present as risk factors for the development of cardiac diseases. No significant changes have been observed in other aspects of lipid profile.[16]

CONCLUSION

In our study, we have found significant changes in blood glucose, TAG and VLDL in patients who underwent inhaled corticosteroid therapy for six weeks. We were also able to record a significant improvement in the pulmonary function tests of these patients after treatment with ICS. Glycated albumin and hsCRP have not demonstrated significant change. Treatment of asthma with inhaled corticosteroids causes a significant numerical rise in levels of glucose, TAG and VLDL. These may present as risk factors for the development of Diabetes mellitus and cardiac diseases with other co-morbid conditions along with prolonged use of ICS. Estimation of glycated albumin and hsCRP might not be useful as markers during short-term use of ICS. However long-term use may produce significant results.

LIMITATIONS

The sample size was small. IgE and Eosinophil count along with other immunological parameters could have also been measured. C-peptide and insulin could have been measured to evaluate the presence of insulin resistance.

ACKNOWLEDGEMENT

This study was supported by ICMR-STS (Indian council of medical research). We thank all laboratory technicians for their support.

REFERENCES

1. National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy ClinImmunol, 2007; 120(Suppl): S94–138.
2. Buyukozturk S, Gelincik AA, Genç S, Koçak H, Oneriyidogan Y, Erden S, et al. Acute phase reactions in allergic airway disease. Tohoku J Exp Med., 2004; 204: 209-13.
3. Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera E, Palosuo T. The association of sensitive systemic inflammation markers with bronchial asthma. Ann Allergy Asthma Immunol, 2002; 89: 381-5.
4. Fujita M, Ueki S, Ito W, Chiba T, Takeda M, Saito N, et al. C-reactive protein levels in the serum of asthmatic patients. Ann Allergy Asthma Immunol, 2007; 99: 48-53.
5. Kony S, Zureik M, Driss F, Neukirch C, Leynaert B and Neukirch F. Association of bronchial hyperresponsiveness and lung function with C - reactive protein (CRP): a population based study. Thorax, 2004; 59: 892-6.
6. Kasayama S, Tanemura M, Koga M, Fujita K, Yamamoto H, Miyatake A. Asthma is an independent risk for elevation of plasma Creactive protein levels. Clin Chim Acta, 2009; 399: 79-82.
7. Takemura M, Matsumoto H, Niimi A, Ueda T, Matsuoka H, Yamaguchi M, et al. High sensitivity C-reactive protein in asthma. Eur Respir J., 2006; 27: 908-12.
8. Schou AJ, Wolthers OD. Serum Fructosamine, Total Cholesterol, and High-Density Lipoprotein in Children with Asthma during Glucocorticoid Treatment. ISRN Allergy., 2011; 2011: 295124.
9. Björntorp P. Hormonal control of regional fat distribution. Hum Reprod., 1997 Oct; 12Suppl 1: 21–5.
10. Kiviranta K and Turpeinen M. Effect of eight months of inhaled beclomethasonedipropionate and budesonide on carbohydrate metabolism in adults with asthma. Thorax., 1993; 48(10): 974–978.
11. Ebden P, McNally P, Samanta A and Fancourt GJ. The effects of high dose inhaled beclomethasonedipropionate on glucose and lipid profiles in normal and diet controlled diabetic subjects. Respiratory Medicine, 1989; 83(4): 289–291.
12. A.J. Schou and O.D. Wolthers, "Serum fructosamine, total cholesterol and high density lipoprotein in children with asthma during glucocorticoid treatment," ISRN allergy., 2011; 2011: 295124.
13. Rakesh Lodha and S K Kabra, "Do inhaled corticosteroids adversely influence glucose metabolism?," Indian Pediatrics., 2009; 46: 293-4.
14. Francis Egbuonu, Farrah A Antonio and Mahamood Edavalath, "Effect of inhaled corticosteroids on glycemic status," Open Respir Med J., 2014; 8: 101–5.
15. Luttjohann, Jarrod R., "Do Inhaled Corticosteroids Cause an Increased Risk for Developing or Worsening a Patient's Diabetes Mellitus?", PCOM Physician Assistant Studies Student Scholarship, 2012; 55.
16. J. R. Mead, S. A. Irvine and D. P. Ramji, "Lipoprotein lipase: Structure, function, regulation and role in disease," Journal of Molecular Medicine, 2002; 80(12): 753-69.