

Hemoglobin A1c Levels in Children with Asthma Using Low Dose Inhaled Corticosteroids

*OYA YÜCEL, YESİM EKER, CAGATAY NUHOGLU AND OMER CERAN

From *Baskent University, Medical Faculty, Istanbul, Turkey; and Department of Pediatrics, Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey.

Correspondence to: Dr Oya Yücel, Kosuyolu, Veysi Pasa Sok. 100. Yil Sitesi, I Blok, No: 22, Üsküdar, Istanbul, Turkey. E-mail: oyayucel2000@yahoo.com

Manuscript received: April 24, 2007; Initial review completed: October 30, 2007;

Revision accepted: May 26, 2008.

Objectives: Steroids may raise the blood glucose levels as a systemic effect. Due to this, the potential effect of prophylactic use of inhaled steroids (ICS) on HbA1c levels in children with asthma was investigated.

Study design: Case control study.

Setting: Outpatient department.

Participants: 141 children with asthma but without diabetes (study group) and 52 children without diabetes or asthma (control group).

Main outcome measure: HbA1c levels.

Results: The mean age of the study group ($n=141$) was 6.6 ± 3.0 years and comprised 70 females (50% of the group) and 71 males. The mean age of the control group

($n=52$) was 7.1 ± 3.0 years, and comprised 24 females (46%) and 28 males (54%). Age and sex differences between the groups were not significant. The mean HbA1c value was $5.44\pm 0.75\%$ among the children with asthma and $5.14\pm 0.41\%$ in the control group. HbA1c levels in children with asthma was significantly higher than the control group ($P=0.006$). No significant correlation was found between cumulative dose of ICS and HbA1c levels. Similarly, levels of HbA1c did not change with increased time of usage of ICS ($P=0.96$).

Conclusion: Asthmatic children who are taking low doses of ICS have higher HbA1c values than healthy children.

Key words: Bronchial asthma, Children, Corticosteroids.

Inhaled corticosteroids (ICS) are the preferred treatment in children of all ages with persistent asthma(1-3). Chronic use of ICS improves long-term outcomes for children of all ages with mild or moderate persistent asthma. However, chronic use of ICS may result in adverse systemic effects(4).

Hemoglobin A1c (HbA1c) levels provide an indication of the average blood glucose concentration during the preceding 2-3 months(5,6). Many studies have emphasized that blood glucose levels increase in asthmatic children using high doses of inhaled or oral corticosteroids(4,7). There is no report in the literature addressing the issue of long term glycemic control in these children. We aimed to study the levels of HbA1c in children with persistent asthma using prophylactic doses of ICS.

METHODS

This study was undertaken over a period of one year in the outpatient Pediatric Asthma and Allergic Diseases Clinic in Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey. One hundred forty one children from 3 through 12 years of age with mild persistent asthma (70 females and 71 males) and who had no diabetes were enrolled in the study group. Fifty two healthy children (24 females and 28 males) were assigned to the control group. Children who were diagnosed with mild persistent asthma according to the GINA report guidelines were eligible for inclusion(3).

Accompanying Editorial: Pages 293-94

We included children who had controlled asthma and were using low doses of ICS for at least previous

6 months. We considered low dose ICS as receiving budesonide 200-400 μ g bid or fluticasone propionate 125-250 μ g bid. Children on oral corticosteroids were excluded. Subjects were excluded if they had a recent acute asthmatic attack, or were having co-existing pulmonary or cardiac disease. A PPD test was given to all children. If the level of the PPD test result was pathologic, children were excluded from the study.

In children using low doses of ICS for at least 6 months, HbA1c levels were measured and the cumulative doses of ICS were calculated. We also provided each patient with bronchodilator medication as needed. The parents of patients were requested to fill in a questionnaire regarding family and personal history of atopic diseases (eczema, urticaria, allergic rhinitis, asthma) to determine minor or major risk factors according to the GINA report(3), and information was obtained about the presence of diabetes mellitus and asthma in first and second degree relatives.

The study was conducted according to principles of the Declaration of Helsinki (1989). Informed consent was obtained from all people after full explanation of the study.

In each case, venous blood samples were collected in tubes containing EDTA. Blood samples were obtained in the early morning under fasting conditions as a standard procedure. HbA1c was measured using a dedicated TINA (turbidimetric inhibition immunoassay-Roche Hitachi Modular Rutin Otoanalyzer). Reference values for healthy control subjects were 5.0-8.0%.

Analysis was done using the SPSS version 12.0. All values were expressed as a mean \pm standard deviation. The obtained results were compared between the groups by independent samples test. Correlations were calculated with the Pearson test. $P<0.05$ was considered significant.

RESULTS

In the study group ($n=141$), the mean age was 6.6 \pm 3.0 years, and 51% ($n=71$) were male. In the control group ($n=52$), the mean age was 7.1 \pm 3.0 years and 24 of them (46.2%) were female. No

significant age and sex differences were found between the study and control groups ($P=0.33$, $P=0.66$, respectively).

The prevalence of asthma in relatives was more commonly present among the children with asthma than the control group ($P<0.001$). The prevalence of type2 diabetes mellitus was more commonly present among the second degree relatives of children in the control group ($P=0.05$; 95% confidence interval, $-0.27-0.001$).

The mean HbA1c level in the study group was 5.44 \pm 0.75%. The mean HbA1c level in the control group was 5.14 \pm 0.41% ($P<0.01$; 95% confidence interval, 0.089-0.52). When we evaluated our patients according to using of beta agonists, the average level of HbA1c was 5.46 \pm 0.26% in the patients using beta agonists in last 6 months and 5.53 \pm 0.52% in patients not using beta agonists ($P=0.49$). About 75% of our patients with asthma were receiving budesonide and 25% fluticasone propionate. Prior to the enrolment, the patients had been using ICS for at least six months. The children taking budesonide or fluticasone propionate were evaluated separately. The average HbA1c level of the patients taking only budesonide was 5.49 \pm 0.47% and the average HbA1c level of the patients taking only fluticasone propionate was 5.65 \pm 1.72%. There was no statistically significant difference between the two groups ($P=0.50$). The average of total cumulative value for budesonide was 112957.6 \pm 135749.8 μ g and for fluticasone propionate was 68368.4 \pm 70900.9 μ g. There was no correlation between cumulative doses of ICS and HbA1c levels in children with asthma ($P=0.91$, $r=0.013$). Average time of ICS usage was 13.5 \pm 12.7 months. There was no correlation between duration of ICS usage and HbA1c levels ($P=0.96$, $r=0.005$).

DISCUSSION

Many studies researching oral or high dose ICS are found in the literature. Systemic adverse effects of administration of ICS are emphasized in these studies, but there remains a certain degree of uncertainty concerning the effects of long term administration of low doses(1,4,8,9). In our study, HbA1c levels were found to be higher in asthmatic children than healthy controls. The findings also

WHAT IS ALREADY KNOWN?

- Inhaled corticosteroids are the best choice for initial therapy of asthma.

WHAT THIS STUDY ADDS?

- Asthmatic children who are taking low doses of inhaled corticosteroids have higher HbA1c values than healthy children.

showed that the effects of the two medicines (budesonide and fluticasone propionate) on the blood glucose at prophylactic doses are similar. Sathiyapriya, *et al.*(10) showed that HbA1c concentrations increased significantly in the non-diabetic adult patients with asthma. In addition they pointed out that they could find no study concerning HbA1c concentrations in children with asthma. We also found that duration of ICS usage was not an important factor for affecting HbA1c levels.

Mean blood glucose level was calculated from HbA1c levels by using a formula in accordance with Rohlfing, *et al.*(11) ($\text{HbA1c} \times 35.6 - 77.3 = \text{mg/dL}$ or $\text{HbA1c} \times 1.98 - 4.29 = \text{mmol/L}$). According to this formula, the approximate mean blood glucose concentration was found to be 117 mg/dL (6.5 mmol/L) in our patients receiving ICS, and 106 mg/dL (5.89 mmol/L) in the control group. The clinical significance of this difference is uncertain.

Long-term use of ICS in children with asthma may be associated with a variety of side effects, similar to those observed with systemic corticosteroid therapy. The average blood glucose level can be affected in children using prophylactic doses of ICS. The high blood glucose level can be one of the systemic side effects in children receiving prophylactic doses of ICS for at least 6 months. So, the development of adverse effects of ICS therapy is dependent on the dose, frequency and duration of these drugs(1). Limited pharmacokinetic data are available to define the pulmonary absorption characteristics of budesonide. Evidence from a population analysis shows that the pulmonary absorption of budesonide is prolonged and has wide interindividual variation(12,13). Brutche, *et al.*(7) investigated the absorption of ICS in patients with different severities of asthma receiving different doses. Systemic availability of fluticasone

propionate was found to be substantially less in patients with moderate to severe asthma than in healthy controls. Although fluticasone propionate and budesonide are widely used, they are not without systemic side effects(1,2).

Our study had certain limitations. Direct estimates of the adverse effects of long term use of ICS based on studies in humans are difficult to interpret. Diabetic children with asthma who were treated with beta agonists had significantly better glycemic control than children with diabetes alone(14). However, other studies showed that high-dose nebulized salbutamol significantly increased mean blood glucose levels(7,15). We also recommend each patient to use beta agonists as needed. Nonetheless, when we evaluated our patients in the study group according to using of beta agonists, we could not find any relationship between use of beta agonist and HbA1c levels. Some patients were using a leukotriene antagonist, but this also did not affect our HbA1c results. Even if beta agonists tend to produce hyperglycemia, they have not been used for a long enough period of time in order to change the level of HbA1c in our patients. But the glycemic effects of salbutamol were not included in our research data. Therefore, new studies might be necessary to investigate this effect.

ACKNOWLEDGMENT

We acknowledge the help of Asso Prof Mustafa Yildiz for statistical analysis.

Contributors: YO had primary responsibility for protocol development, patient screening, enrolment, outcome assessment, preliminary data analysis and writing the manuscript. EY participated in the development of the protocol, data collection, enrolment and writing of the manuscript. NC participated in the statistical analysis and outcome assessment. CO participated to outcome assessment.

Funding: None.

Competing interests: None stated.

REFERENCES

1. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma update on selected topics-2002. *J Allergy Clin Immunol* 2002; 110: 141-219.
2. The Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. *Control Clin Trials* 1999; 20: 91-120.
3. Global Initiative for Asthma (GINA). Workshop report, global strategy for asthma management and prevention (updated November 2006). Available at: <http://www.ginasthma.com/Guidelineitem.aspx?l1=2&l2=1&intId=60>. Accessed April 20, 2007.
4. Allen DB. Systemic effects of inhaled corticosteroids in children. *Curr Opin Pediatr* 2004; 16: 440-444.
5. Eldeirawi K, Lipton RB. Predictors of hemoglobin A1c in a National Sample of Nondiabetic Children. The Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol* 2003; 157: 624-632.
6. Osterman-Golkar SM, Vesper HW. Assessment of the relationship between glucose and A1c using kinetic modeling. *J Diab Comp* 2006; 20: 285-294.
7. Brutsche MH, Brutsche IC, Munawar M, Langley SJ, Masterson CM, Daley-yates PT, *et al.* Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet* 2000; 356: 556-561.
8. Drake AJ, Howells RJ, Shield JPH, Prendiville A, Wards PS, Crowne EC. Symptomatic adrenal insufficiency presenting with hypoglycaemia in asthmatic children with asthma receiving high dose inhaled fluticasone propionate. *BMJ* 2002; 324: 1081-1083.
9. Smith AP, Banks J, Buchanan K, Cheong B, Gunawardena KA. Mechanisms of abnormal glucose metabolism during the treatment of acute severe asthma. *Q J Med* 1992; 82: 71-80.
10. Sathiyapriya V, Bobby Z, Kumar SV, Selvaraj N, Parthibane V, Gupta S. Evidence for the role of lipid peroxides on glycation of hemoglobin and plasma proteins in non-diabetic asthma patients. *Clin Chim Acta* 2006; 366: 299-303.
11. Rohlffing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA1c, Analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial. *Diabetes Care* 2002; 25: 275-278.
12. Harrison TW. Systemic availability of inhaled budesonide and fluticasone propionate: healthy versus asthmatic lungs. *Bio Drugs* 2001; 15: 405-411.
13. Donnelly R, Seale JP. Clinical pharmacokinetics of inhaled budesonide. *Clin Pharmacokinet* 2001; 40: 427-440.
14. Wright NP, Wales JK. The incidence of hypoglycaemia in children with type 1 diabetes and treated asthma. *Arch Dis Child* 2003; 88: 155-156.
15. Dawson KP, Pena AC, Manglick P. Acute asthma, salbutamol and hyperglycaemia. *Acta Pediatr* 1995; 84: 305-307.