Lung function abnormalities in children with type 1 diabetes

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Abstract Recent developments in intrabronchial administration of insulin raise lung function in patients with type 1 diabetes as important issue. Several studies in adults report abnormalities of lung function of these patients. The aim of this study was to investigate lung function in children with type 1 diabetes.

Twenty-seven children with type 1 diabetes performed measurement of airway obstruction (forced flow-volume curves), lung volumes and airway resistance (bodyplethysmography) and of pulmonary carbon monoxide diffusion capacity.

Mean age (±SD) of the children was 12.8 ± 5 years. Mean time between the detection of type 1 diabetes and the lung function tests was 5.5 years with a variation from 1 to 17 years. The total airway resistance (Raw) was significantly higher compared to the reference values (P < 0.001). The other lung function parameters were not significantly different from reference values (P > 0.05). In this relatively small study no relationship between lung function abnormalities and age, the duration of disease or level of HbA1c was observed.

Our data show that increase of airway resistance do occur in children with type 1 diabetes. Progressive abnormalities in lung function might interfere with the promising results of treatment with intrabronchial administration of insulin.

INTRODUCTION

Inhaled insulin therapy in diabetics has been tried for more than 25 years, but became only recently successful in clinical trials of patients with type 1 diabetes (1). Subsequent correspondence on this topic made it clear that the safety of inhaled insulin with regard to cardiac and lung function should be considered (2). Lung function is extremely important for optimal drug deposition as exemplified by patients with asthma or chronic obstructive lung disease (COPD). Therefore, the study of lung function in type 1 diabetes deserves new attention.

Several studies in adults with type 1 diabetes report abnormalities in lung function of these patients. Reduced lung volumes (3,4), and a reduced carbon monoxide diffusion capacity have been described (3–5).

To our knowledge, there are only a few studies into lung function abnormalities in children with type 1 diabetes. Two studies showed significant reduction of lung volumes (forced vital capacity, FVC) in diabetic children compared to reference values (6,7). One study showed significant increase of airway resistance (Raw) and normal lung volumes in children with type 1 diabetes (8). Carbon monoxide diffusion capacity (DLCO) was not studied in children until now. Because of the scarcity of data in children with type 1 diabetes and the importance of lung function for proper pulmonary drug delivery, we studied the lung function more extensively.

PATIENTS AND METHODS

Twenty-seven patients with type 1 diabetes were recruited from the endocrinology outpatient department of the Wilhelmina Children’s Hospital. None of the
patients had a history of lung disease and all were non-smokers. None of them used inhaled insulin.

All patients performed maximal expiratory flow volume curves, with use of a pneumotachometer system with a Lilly head (MasterScreen Pneumo, Erich Jaeger, Würzburg, Germany). These curves provide data on airway obstruction (forced expiratory volume in l/s, FEV₁) and on lung volume (FVC). Total lung capacity (TLC), residual volume (RV) and Raw were measured in a body plethysmograph (Masterlab, Erich Jaeger, Würzburg, Germany). For reference values data of Zapletal were used (9). Carbon monoxide diffusion capacity, corrected for alveolar volume (DLco/VA) was measured using a standardised single breath technique (Masterlab, Erich Jaeger, Würzburg, Germany). Reference values for DLco/VA for healthy Dutch children were used (10). All lung function measurements were performed according to the ATS/ERS standards.

Results are presented as mean values of percentage of predicted ± SD. For comparison with normal values one sample t-tests were used. To study correlation between lung function and age, duration of disease and HbA₁c a Spearman rank correlation test was used. The study was approved by the hospital medical ethics committee.

RESULTS

Mean age of the children was 12.8 ± 5.0 years. Mean time between the detection of type I diabetes and the lung function tests was 5.5 years with a variation from 1 to 17 years. Mean HbA₁c was 8.5% with a variation from 6 to 16.9%.

Mean FEV₁ was 109 ± 12% of the predicted values, FVC 103 ± 12%, TLC 100 ± 12%, RV 105 ± 36%, DLco/VA 119 ± 20%. These lung function parameters were not significantly different from reference values (p > 0.05), and all values were within the 95% confidence intervals. Mean Raw 136 ± 49%, which was significantly higher compared to the reference values (p < 0.001). Raw values in nine children were above the 95% confidence interval.

We found no statistically significant correlation between lung function values and age, disease duration or HbA₁c.

DISCUSSION

In our group of children with type I diabetes we found a statistical significant increase of total airway resistance (Raw), while lung volumes, FEV₁ and carbon monoxide diffusion capacity were normal. In this relatively small study we could not find a correlation between lung function values and age, disease duration or HbA₁c. However, this study shows that even in children with a relatively short history of type I diabetes, pulmonary abnormalities may exist.

The most important finding of our study was an increase of airway resistance, which is in line with the findings in another group of children with type I diabetes, described by Verrotti et al. (8). Although several studies on lung function in adults with type I diabetes are described, only few authors measured airway resistance. In one small study with 11 patients between 21 and 28 years of age Raw was increased compared to normal controls, but the difference did not reach statistical significance (11).

The explanation for increase of airway resistance is unclear. In adults with type I diabetes increased glycosylation of tissue proteins has been described, which can result in increased cross-linkage of collagen and elastin (12). Increased cross-linkage of tissue proteins in the lungs might explain the stiffer behaviour of the airways and the increase of airway resistance. In adult patients with type I diabetes thickening of the basal membrane has been described (13), which also might result in increased airway resistance. Whether this phenomenon also plays a role in children in unknown. Recent studies have shown the success of administration of insulin in the bronchial tree (1,2). In general, the efficacy of drug delivery by aerosol largely depends on the inspiratory flow rate that can be achieved by a patient. Increase of airway resistance can decrease inspiratory flow rates. This argues for further studies into the airway resistance in children and adults with type I diabetes, because bronchial pathology and increase of airway resistance might interfere with proper deposition and absorption of intrabronchial insulin.

Several studies in adult patients with type I diabetes show a decrease of lung volumes (FVC and TLC, 3,4). The prevalence of restrictive lung disease in adults suggests that this phenomenon might be related to the duration of diabetes. Whether these restrictive abnormalities result from pulmonary or extrapulmonary pathology and whether these abnormalities are preceded by increased airway resistance is unknown. Decrease of respiratory muscle function has been suggested (14), but longitudinal data are lacking.

In our study values of FVC and FEV₁ were in the normal range, which is in line with data in children described by Verrotti et al. (8) Two other studies in children described decreased vital capacity and normal values of FEV₁ (6,7). Maybe recent treatment regimens are more effective in preventing early lung damage.

Several studies in adults with type I diabetes have shown decreased diffusion capacity of carbon monoxide (5), while data in children are lacking. Decreased diffusion capacity points to interstitial lung pathology with thickening of the alveolo-capillary membrane. We did not find diffusion disturbances in our young patients. It has been suggested that diffusion abnormalities are due to the development of pulmonary microangiopathy (12). Progressive pulmonary microangiopathy may cause
decreased carbon monoxide diffusion capacity in patients with advanced type I diabetes. This is an important finding, because it has been shown that intensive therapy effectively delays the onset of microangiopathy and slows the progression of diabetic retinopathy, nephropathy and neuropathy.

When studying lung function in children it is important to compare the results with adequate reference values. While reference data in Dutch children are lacking, usually the reference data of Zapletal are used (9,15). Although the mean spirometric results were above 100% predicted, all patients had results within the 95% confidence intervals. One-third of patients had Raw values above the 95% confidence interval, which suggests a real increase of Raw in a significant proportion of our children (15).

Our data show that increase of airway resistance do occur in children with type I diabetes. Data in literature suggest increase of lung function abnormalities during later life, especially decrease of lung volumes and carbon monoxide diffusion capacity. A long-term follow-up study in larger groups of patients is needed to describe the relationship between lung function abnormalities and the duration and severity of the disease. Progressive abnormalities in lung function might interfere with the promising results of treatment with intrabronchial administration of insulin.

REFERENCES