Evaluation of pulmonary function changes in children with type 1 diabetes mellitus in Upper Egypt

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Abstract

Background: Diabetes mellitus is a leading cause of morbidity and mortality among children across the world and is responsible for a growing proportion of global healthcare expenditure. However, limited data are available on lung dysfunction in children with diabetes.

Aim: The aim of this study was to evaluate the pulmonary function changes in children with type 1 diabetes mellitus (T1DM).

Methods: We studied 60 children with T1DM (mean age 10.5 ± 2.32 years; disease duration 2.45 ± 0.6 years, and 50 healthy control children (mean age 9.9 ± 2.5 years). Spirometry was performed for all individuals to measure forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, and peak expiratory flow rate (PEFR). Glycemic control was assessed on the basis of glycated hemoglobin (HbA1c), with HbA1c values $<8\%$ considered to indicate good glycemic control, and HbA1c values $\geq 8\%$ to indicate poor control.

Results: There was significant reduction in all spirometric parameters in diabetic children in comparison with healthy control children. Children with poor glycemic control had significant impairment in lung functions compared with those with good glycemic control.

Conclusions: T1DM in children leads to impairment of lung functions and this impairment increases with poor glycemic control.

Keywords: children, Egypt, pulmonary function, spirometry, type 1 diabetes mellitus

Introduction

Diabetes mellitus is a chronic progressive disease that has profound consequences for individuals, families and society. Chronic complications in diabetes mellitus are mostly due to macrovascular and microvascular damage and include cardiovascular disease, nephropathy, retinopathy, diabetic neuropathy and lung damage, though the pulmonary complications of diabetes mellitus have been poorly characterized. Few studies had addressed abnormalities of lung functions in children with type 1 diabetes mellitus (T1DM) which included a mild decrease in vital capacity, decreased or normal forced vital capacity (FVC) and slightly increased airway resistance [Unger, 2008; Bollou *et al.* 2003; Primhak *et al.* 1987; Cazzato *et al.*

2004; Villa *et al.* 2004]. Pulmonary impairment in diabetic patients arises from changes in collagen and elastin connective tissue and diabetic microangiopathy. As the lung has abundant connective tissue and diffuse microvascular circulation, it is thought to be a target organ for diabetic disease. Because the pulmonary function and gas exchange depend on the integrity of the connective tissue and microcirculation within the lung, abnormalities involving these components could lead to mechanical lung dysfunction and impaired blood gas exchange. Studies conducted in adult patients with T1DM report diminished elastic lung recoil, reduced lung volumes and altered alveolocapillary diffusion [Villa *et al.* 2004; Cooper *et al.* 1990; Innocenti *et al.* 1994; Isotani *et al.* 1999].

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In addition, the increased systemic inflammation associated with diabetes may result in pulmonary inflammation and hence airway damage. Moreover, hyperglycemia can cause a secondary reduction in antioxidant defense of the lungs and increased susceptibility to environmental oxidative insults with subsequent loss of respiratory function [Al-Saadi *et al.* 2011; Walter *et al.* 2003; Brownlee, 2001].

In the current study, we aimed to evaluate changes in the pulmonary functions in pediatric patients with T1DM in Upper Egypt and to study the relationship of these changes, if any, to glycemic control.

Patients and methods

This study was conducted in the outpatient diabetic clinic at Pediatric Assiut University Hospital, Egypt. Approval of the ethical committee was obtained and all enrolled patients completed a written consent form. A total of 60 T1DM patients who were otherwise healthy were randomly selected with their age ranged from 6 to 16 years. Those patients were matched with another group of 50 control healthy subjects in the terms of age, height, weight, body mass index (BMI) and socioeconomic status. Patients with T1DM were further divided into two groups: (1) well controlled cases (28 patients); and (2) poorly controlled diabetes mellitus (32 patients).

Glycemic control in patients was evaluated by high-performance liquid chromatography (HPLC) (DIAMAT, Bio-Rad, Munich, Germany) of glycated hemoglobin (HbA1c) every 3 months during the year preceding the study. According to Assiut University Children hospital guidelines and other researchers [Villa *et al.* 2004; American Diabetes Association, 1990], mean HbA1c values <8% were considered to indicate good glycemic control while HbA1c values ≥8% were considered to indicate poor control. Standard spirometry was performed in all individuals by mean of a fully equipped computerized system (Cosmed SrL, Quark PFTs ergo, P/N Co9035–12–99, Italy). All pulmonary function tests were carried out at a fixed time of the day in the morning (9.00–12.00 hours) to minimize diurnal variation [American Thoracic Society, 1995]. Each subject was informed about the whole maneuver and was encouraged to practice it before testing. The apparatus was calibrated daily and operated within the ambient temperature range of 20–25°C. The

precise technique for the present study was practiced with reference to the official statement of the American Thoracic Society on the standardization of spirometry [American Thoracic Society, 1995]. The tests were repeated three times after adequate rest. The best result of three reproducible tests was taken. The parameters that were measured included FVC, forced expiratory volume in 1 second (FEV1), forced expiratory ratio (FEV1/FVC) and peak expiratory flow rate (PEFR).

Exclusion criteria

Subjects with gross abnormalities of the vertebral column, thoracic cage, restricted joint mobility, known history of acute or chronic respiratory infections, neuromuscular disease, malignancy and cardiopulmonary disease, and those who had undergone major abdominal or chest surgery were excluded from the study. In addition, subjects with current or previous drug or tobacco history were excluded. Patients with known complications of diabetes mellitus such as diabetic neuropathy, nephropathy and retinopathy were also excluded from the study.

Statistical analysis

Statistical analysis was carried out using SPSS (Statistical Package for Social Sciences), version 16. Data were presented as mean ± standard deviation (SD). The Mann–Whitney and unpaired *t*-test were used to compare groups; *p* values ≤0.05 were considered significant.

Results

In this study, 60 children (32 males and 28 females) and 50 controls (29 males and 21 females) were recruited. The demographic data, duration of the disease, glycemic control and lipid profile are shown in Table 1. All spirometric lung function parameters (FVC, FEV1, FEV1/FVC and PEF) were significantly lower in diabetic children than controls (Table 2). As regards to glycemic control, Table 3 shows that only FEC and FEV1 were significantly lower in children with poor glycemic control than those with good control.

Discussion

T1DM is one of the most common endocrine and metabolic conditions in childhood. Data on the incidence of childhood-onset T1DM are limited.

Table 1. Demographic data and chemical profiles of children with type 1 diabetes mellitus (T1DM) and control subjects.

Parameter		Patients with T1DM (mean $\pm$ SD) <i>n</i> = 60	Controls (mean $\pm$ SD) <i>n</i> = 50	<i>p</i> value
Sex	Male	32	29	NS
	Female	28	21	NS
Age (years)		10.5 $\pm$ 2.32	9.9 $\pm$ 2.5	NS
Duration of diabetes mellitus		2.45 $\pm$ 0.6	–	–
HbA1c (%)		10.9 $\pm$ 2.3	4.6 $\pm$ 0.28	< 0.002

HbA1c, glycated hemoglobin; NS, not significant.

Table 2. Spirometric findings in children with T1DM compared with control group.

Parameter		Patients with T1DM (mean $\pm$ SD) <i>n</i> = 60	Controls (mean $\pm$ SD) <i>n</i> = 50	<i>p</i> value
VC		1.86 $\pm$ 0.81	2.45 $\pm$ 0.63	<0.0001
FVC in		1.54 $\pm$ 0.83	2.45 $\pm$ 0.63	<0.0001
FVC ex		1.80 $\pm$ 0.79	2.38 $\pm$ 0.68	<0.0001
FEV 1		1.66 $\pm$ 0.74	2.02 $\pm$ 0.54	<0.002
FEV1/VC (%)		89.2 $\pm$ 8.8	84.3 $\pm$ 0.63	<0.02
FEV1/ FVC		92.6 $\pm$ 8.6	85.9 $\pm$ 0.4	<0.001
PEF		3.2 $\pm$ 0.3	5.98 $\pm$ 0.9	<0.02

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow rate; T1DM, VC, vital capacity.

Data from large epidemiological studies worldwide indicate that, on an annual basis, the overall increase in the incidence of T1DM is around 3% and about 78,000 children under age 15 years develop T1DM worldwide [Berhan, 2014]. Among Eastern Mediterranean and Middle Eastern countries, the largest contribution to the total number of estimated childhood T1DM cases comes from Egypt, which accounts for about a quarter of the region's total with an incidence 8/100,000 per year in Egyptian children under the age of 15 years [International Diabetes Federation, 2013; El-Zanaty and Way, 2008].

In our study HbA1c was significantly higher in children with T1DM compared with healthy controls. This may be explained by possible lack of compliance with insulin dosage, irregular or sub-dosing of insulin, or maybe overeating and lack of a diabetic lifestyle [Ramirez *et al.* 1991]. Higher levels of HbA1c are an indicator of poor diabetic control, which means a higher level of circulating glucose. If circulating glucose is constantly at a

higher level, it can lead to more and more non-enzymatic glycosylation of tissue proteins. The respiratory system is one of the targeted tissues of this glycosylation [Ramirez *et al.* 1991], which is reflected in the results of the current study. Our study showed significant reduction in spirometric parameters in diabetic children compared with healthy controls. Moreover, children with poor glycemic control had significant impairment in lung function than those with good glycemic control. Cazzato and colleagues conducted a cross-sectional study to assess the pulmonary function in children with T1DM and reported that FVC and FEV1 were found to be significantly lower in diabetics than in healthy controls [Cazzato *et al.* 2004]. Innocenti and colleagues reported that diabetic patients had a reduced FVC and FEV1 compared with their matched controls [Innocenti *et al.* 1994]. These findings are in agreement with previous reports [Gajbhiye and Tambe, 2013; Benbassat *et al.* 2001]. It was reported that even in children with a relatively short history of T1DM, pulmonary abnormalities

Table 3. Comparison between well controlled and poorly controlled cases with T1DM.

Parameter	Well controlled group (1)	Poorly controlled group (2)	p value
	n = 28	n = 32	
VC	2.16 ± 0.68	1.43 ± 0.54	<0.001
FVC in	1.67 ± 0.81	1.45 ± 0.71	NS
FVC ex	2.06	1.64	NS
FEV 1	1.95 ± 0.85	1.45 ± 0.62	<0.01
FEV1/VC	88.6 ± 9.3	87.3 ± 0.7	NS
FEV1/FVC	89 ± 7.9	90 ± 0.5	NS
PEF	4.5 ± 0.6	3.8 ± 0.24	NS
Duration of diabetes mellitus	3.1 ± 0.8	2.8 ± 0.7	NS

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NS, not significant; PEF, peak expiratory flow rate; T1DM, VC, vital capacity.

may exist [van Gent *et al.* 2002]. Rosenecker and colleagues reported that children with T1DM had an increase in airway resistance; in addition, FVC and FEV1 were significantly decreased over the 5-year study period, whereas patients without diabetes did not show a significant decline during the study period [Rosenecker *et al.* 2001].

Two main pathophysiologic mechanisms have been proposed as underlying impaired pulmonary function in diabetes. First, because the thorax and lungs are rich in collagen and elastin, nonenzymatic glycation of these structural compounds could cause stiffening of the thorax and lung parenchyma. This may lead to a restrictive pattern. Second, diabetes-related microvascular damage may reside in the lungs in parallel with complications in the kidneys, retina and nerves. A postmortem histologic study indeed showed thickening of both the alveolar epithelial and pulmonary capillary basal laminae in patients with diabetes. Also, reduced pulmonary capillary blood volume was found, suggesting the presence of pulmonary microangiopathy. This could perhaps lead to a redistribution of the pulmonary circulation, potentially causing well-ventilated areas to become under perfused [van den Borst *et al.* 2010; Ofulue and Thurlbeck, 1988; Powers, 2008].

In conclusion; T1DM in children is associated with impairment of lung function and this impairment increases with poor glycemic control. Affection of the respiratory system may have no relation to the duration of T1DM. Further studies with more recruited patient numbers and evaluation of further pulmonary functions rather than

spirometric parameters are needed. Based on the study findings, we recommend that children with T1DM should undergo periodic spirometric evaluation to assess their extent of impaired pulmonary function. This evaluation will help detection of early pulmonary dysfunction and might help prevent further pulmonary decompensation, which over time contributes to pulmonary morbidity and mortality of the disease.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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