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High prevalence of spirometric abnormalities in patients with type 1 diabetes mellitus

Częste występowanie zmian w spirometrii u pacjentów z cukrzycą typu 1

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Abstract

Introduction and aim of the study: To document abnormalities on spirometry in patients with type1 diabetes mellitus (DM) and to study the determinants of these.
Material and methods: Thirty nine patients attending the type 1 DM clinic underwent spirometry. The absolute FEV_1 and FVC were compared with the predicted ones and expressed as a percentage of the predicted. Additional information collected included gender, age, weight, height and the latest glycated hemoglobin. Data were presented as mean±SD. χ^2 test was used to study differences in proportions and Pearson's coefficient was calculated for correlations.
Results: Twenty patients (51.2%) had pulmonary function abnormalities, of which 17 patients had a restrictive pattern on spirometry and 3 had an obstructive pattern. Of all the patients, 45.8% were stunted, i.e. had the height SDS <-2 SD while 25.7% were extremely stunted (height SDS <-3). Seven of 9 (77.8%) patients with extreme stunting (Ht SDS <-3) had restrictive ventilatory disturbances, whereas only 8 of 26 (30.7%) persons with Ht SDS above -3 had the same ($p < 0.05$).
Conclusions: Spirometric abnormalities are common in type 1 DM and stunting is a significant determinant of the same.

KEY WORDS: diabetes mellitus, respiratory function tests, spirometry

Streszczenie

Wprowadzenie i cel pracy: Ocena zaburzeń spirometrycznych u dzieci z cukrzycą typu 1 i czynników im sprzyjających.
Materiał i metody: U 39 pacjentów z cukrzycą typu 1 wykonano badanie spirometryczne. Całkowity FEV1 i FVC porównano z wartościami przewidywanymi i wyrażono w procentach. Dodatkowe dane stanowiły: płeć, wiek, masa ciała, wzrost i wartość HbA_1c. Wyniki przedstawiono jako wartości średnie i odchylenia standardowe. Przy obliczeniach statystycznych zastosowano testy χ^2 i Pearsona.
Wyniki: U 20 pacjentów (51,2%) stwierdzono nieprawidłowości w badaniu spirometrycznym, w tym u 17 o typie restrykcyjnym, a u 3 o typie obturacyjnym. U 45,8% pacjentów stwierdzono niedobór wzrostu (SDS <-2 SD), u 25,7% wartość hSDS wynosiła poniżej 3. Siedmiu z pacjentów z hDDS poniżej -3 (77,8%) miało restrykcyjne zaburzenia przepływu, podczas gdy w grupie z hSDS powyżej -3 występowały one tylko u 8 (30,7%) z 26 pacjentów ($p < 0,05$).
Wnioski: Zaburzenia spirometryczne są częste w cukrzycy typu 1 szczególnie u dzieci z niedoborem wzrostu.

SŁOWA KLUCZOWE: cukrzyca, badania układu oddechowego, spirometria

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Introduction

Although diabetes mellitus (DM) including its type 1 form is a systemic disease involving all organ systems in the body, its effects on the lungs have not been documented in a conclusive manner. Spirometry is a simple non invasive bedside test that evaluates the ventilatory function of the lungs, helps detect abnormalities and classify them into obstructive or restrictive ventilatory disturbances. However, the results of spirometry in type 1 DM have been quite inconsistent with some studies showing no effect, others showing a restrictive ventilatory disturbance and some others having some obstructive features in addition to a predominant restrictive picture [1-11]. Moreover the determinants of lung involvement in diabetes are not clear. We noted that a majority of our type 1 diabetes patients were stunted, thus

demonstrating the long-term adverse impact of diabetes on growth. Such stunting may affect the development of internal organs like the lungs and thus it would be interesting to evaluate its effects on lung function. We therefore proposed to study the impact of type 1 diabetes on spirometric lung function with further evaluation of the determinants of any abnormalities detected, including the effect of stunting.

Material and methods

Patients attending type1 diabetes clinic of a tertiary care teaching hospital were included in the study after informed consent. All the patients were diabetic according to American Diabetes Association (ADA) criteria with age of onset below the age of 20 years and requiring insulin for glycemic control and were thus clinically diagnosed to have type 1 DM [12]. The following information was collected about each patient: gender, date of birth (to calculate the age at the time of the study recruitment), duration of diabetes (in completed months), weight in kilograms, height in centimeters (measured on a stadiometer with the head in the Frankfurt plane) and the latest glycated hemoglobin. Glycated hemoglobin (HbA_1c) was estimated by ion exchange high pressure liquid chromatography using the D-10 Hemoglobin testing system (Biorad Laboratories Incorporation, CA, USA.). A chest Roentgenogram in posterior – anterior (PA) view was performed in all the patients.

The patients then underwent spirometry on the Morgan Transfer Test Benchmark PFT System (Morgan Scientific Inc., Haverhill, MA, USA.) in accordance with the American Thoracic Society standards as described previously [13, 14]. The following parameters were recorded: forced vital capacity (FVC) in litres, forced expiratory volume in 1st second (FEV_1) in litres and the ratio of $FEV1_1$ to FVC (FEV_1/FVC).The best of three such forced expiratory records were taken for the study.

The absolute FEV_1 and FVC were compared with the FEV_1 and FVC predicted based on height, age and gender and thereby expressed as a percentage of predicted. A restrictive ventilatory disturbance was diagnosed when the FVC was less than 80% of the predicted ratio but the FEV_1/FVC ratio was greater than 0.7. This was further graded as mild (FVC 60-80% of the predicted), moderate (FVC 40-59% of the predicted) and severe (FVC <40% of the predicted) restriction.

An obstructive ventilatory disturbance was diagnosed when the FEV_1 was low (i.e. <80% of the predicted) in the presence of a normal FVC (>80% of the predicted) or when the FEV_1/FVC ratio was <0.7. These were further graded as mild, moderate and severe (FEV_1 60-80%, 40-59% and <40% of the predicted respectively). Data were presented as mean±SD. χ^2 test was used to study differences in proportions and Pearson's coefficient was calculated for correlations. Statistical analysis was performed on SPSS version 13.

Results

A total of 39 patients with type 1 DM were recruited into the study between 2006 to 2009. The mean age of the patients at the time of recruitment was 13.8±6.4 years (min-max 7 to 28 years). Twenty six (66.7%) were girls. BMI was 16±2.4 kg/m^2 and HbA_1c was 11.6±2.7 (min-max 6 to 19%). The mean duration of diabetes was approximately 3 years (min-max 6 months to 12.5 years). Fifteen (38.5%) patients had new onset diabetes (duration ≤1 year). Height standard deviation score (SDS) was -1.8±2.18 (min-max -7.04 to +1.72). Of all the patients, 45.8% were stunted, i.e. had a height SDS <-2 SD while 25.7% were extremely stunted (height SDS <-3). The Chest Roentgenogram was normal in all the patients.

Twenty patients (51.3%) had pulmonary function abnormalities in our study group. Three patients had an obstructive ventilatory disturbance (2 mild and 1 moderate), while 17 had a restrictive ventilatory disturbance. Of the latter, 11 patients had mild restriction, while moderate restriction was observed in 6 patients.

In the patients with restrictive ventilatory distrurbance there was no significant correlation of FVC with the age of onset, duration of diabetes, height SDS or the glycated hemoglobin levels. Using the χ^2 test the proportion of patients with restrictive ventilatory disturbance did not differ between groups when the type 1 DM patients were stratified by the age of onset (<10 years *vs.* >10 years), duration of diabetes (<5 years *vs.* >5 years), current age (<10 years *vs.* >10 years) or HbA_1c (<10% *vs.* >10%). However 7 of 9 (77.8%) of patients with extreme stunting (Ht SDS below -3) had a restrictive ventilatory disturbance whereas only 8 of 26 (30.7%) persons with Ht SDS above -3 had the same ($p < 0.05\%$).

Detailed literature search on other reports of spirometric abnormalities revealed several studies, that are summarized in tables I and II.

Discussion

There are conflicting reports on the nature of spirometric alterations observed in type 1 DM. Five studies summarized in table I showed no effect on spirometric parameters even though in 3 of them, there were abnormalities in other more subtle non-spirometric pulmonary function parameters including total lung capacity i.e. TLC, diffusion capacity, elastic recoil and dynamic lung compliance at 20 and 60 breaths per minute [1-3]. This suggests that even when spirometry is normal, there may nevertheless be lung involvement in type 1 DM.

However, as summarized in table II, there have been many studies which have shown definite abnormalities in spirometry itself. Indeed, in our study, 20 of 39 patients, i.e. 51.3% had spirometric abnormalities and 17 had a restrictive pattern. As in our study, the predominant abnormality noted in literature was in FVC [1, 6-8]. In many studies, restrictive ventilatory disorder was further supported by other abnormalities noted in non-spirometric parameters like diffusion capacity, TLC, residual volume and functional residual capacity [1-3, 7, 9, 11].

However interstitial lung disease, the most common cause of restrictive spirometry is known to be extremely rare in the pediatric age group. Dinwiddie et al. reported a pre-

Table I: Summary of studies in literature that showed no abnormality in spirometry in patients with type 1 diabetes mellitus
Tabela I: Podsumiowanie badań nie wykazujacych zaburzeń w spirometrii u pacjentów z cukrzyca 1 typu

Study (ref. No.) *Badanie*	Patients *Pacjenci*	Controls *Kontrola*	Tests performed *Wykonywane testy*	Observation of lung function *Obserwacja funkcji płuc*	Impact of patient parameters *Parametry pacjentów*
Schuyler et al./*i wsp.* [1]	11	12	static lung pressure volume curves, lung volumes, spirometry, DL(CO), airway and total pulmonary resistance *krzywe statyczne ciśnienie- objętość objętość płuc, spirometria, DL(CO), opór dróg oddechowych i całkowity opór płuc*	total lung capacity and elastic recoil at low lung volumes significantly less than controls; other parameters of pulmonary function were normal *całkowita pojemnosc i podatność płuc przy niskich objetościach płuc znacząco niższa niż w grupie kontrolnej, pozostałe parametry funkcji płuc prawidłowe*	
Strojek et al./*i wsp.* [2]	31	18	spirometry, specific diffusion capacity and dynamic compliance at 20 and 60 breaths/min *spironetria, specific pojemność dyfuzyjna, podatność dynamiczna przy 20 i 60 oddechach / min.*	no disturbance in spirometric parameters,lower specific diffusion capacity and dynamic compliance at both 20 and 60 breaths/min *brak zaburzeń parametrów w spirometrii, niższa specyficzna pojemnośc dyfuzyjna i podatność dyfuzyjna zarówno przy 20' jak i 60' oodechach na min*	the group of diabetic patients with late complications had lower specific diffusion capacity and dynamic compliance at 20 breaths; the latter was particularly low in patients with poor metabolic control *w grupie pacjentów z DM i poźnymi powiklaniami wykazano niższą specyficzną dynamiczną pojemność dyfuzyjną i dynamiczna podatność przy 20 oddechach, ta ostatnio była szczególnie niska u chorych ze zła kontrola metaboliczna DMc*
Verotti et al./*i wsp.* [3]	68	–	spirometry *spirometria*	all spirometric parameters were normal *wszystkie parametry spirometrii były prawidłowe*	all spirometric parameters were normal even in the presence of microalbuminuria (n=34) *wszystkie parametry spirometryczne były prawidowe nawet przy wystepowaniu mikroalbuminurii (n=34)*
Villa et al./*i wsp.* [4]	39	30	spirometry, N_2 washout, DL(CO), *spirometria, N2 wypłukiwanie, DL(CO)*	normal flows and volumes expressed as a percentage of those predicted, low DL(CO) corrected for the alveolar volume *prawidłowe przepływy i objętości wyrażone jako procent wartości należnej, niska DL(CO, skorygowana dla objętości pęcherzykowych)*	HbA_1c was the sole predictor (negative) of DL(CO) on stepwise multiple regression *HbA_1c była jedynym czynnikiem (negatywnym) DL(CO) w analizie wielostopniowej regresji liniowej*
Schernthaner et al./*i wsp.* [5]	20	20	detailed pulmonary function analysis *szczególowa analiza funkcji płuc*	all parameters of pulmonary function were normal including parameters of lung recoil *wszystkie parametry funkcji płuc były prawidłowe, również parametry podatności płuc*	

DL(CO) – diffusion capacity of the lungs for carbon monoxide / *pojemność dyfuzji płuc dla dwutlenku węgla*
HbA_1c is glycated hemoglobin / *hemoglobina glikowana*

valence of 3.6 per million in the UK and Ireland between 1995 and 1998 [15]. No such data are available from India at present. In comparison our type 1 DM patients had very high prevalence of restriction (17 in 39 patients i.e. 43.5%), particularly those with extreme stunting (7 in 9 patients i.e. 77.8%).

In the study by Makker et al., although the predominant defect was restrictive an obstructive pattern was also noted as evidenced by reduction in flow velocities [8]. A slight increase in airway resistance along with reduced diffusion capacity and TLC was also reported by Schnack et al. while Boulbou et al. reported a reduced FEV_1/FVC ratio in the presence of abnormally reduced FVC and DL(CO) [9, 11]. In our study 3 of 39 patients (i.e. 7.7%) had an obstructive ventilatory disturbance which is not very different from the prevalence of obstructive pathology, chiefly asthma in the pediatric population, both in India and elsewhere. Indeed the prevalence of childhood asthma in our population has variously been reported to be between 0.2 to 15.7% [16]. For this reason in the absence of a control group, it cannot be concluded from our study that there exists any association between the spirometric obstructive recordings and the presence of type 1 DM.

Table II: Summary of studies in literature that showed a definite abnormality in spirometry in patients with type 1 diabetes mellitus
Table II: Podsumowanie badań wykazujacych zaburzenia spirometrii u pacjentów z cukrzycą 1 typu.

Study (ref. No.) *Badanie*	Patients *Pacjenci*	Controls *Kontrola*	Tests performed *Wykonywane testy*	Observation of lung function *Obserwacja funkcji płuc*	Impact of patient parameters *Parametry pacjentów*
Primhak et al./*i wsp.* [6]	88	216	spirometry *spirometria*	reduced FVC in diabetics *obniżona FVC u pacjentów z cukrzycą*	reduced FVC not correlated to duration of diabetes or glycemic control *obniżona FVC nie korelowala z czasem trwania cukrzycy lub kontroli glikemii*
Bell et al./*i wsp.* [7]	28	16	spirometry , lung volumes (by Helium dilution technique) and DL(CO) *spirometria, objetość płuc (techniką rozcieńczenia helu) i DL(CO)*	decreased FVC, FEV_1, TLC, residual volume, functional residual capacity and single breath carbon monoxide transfer factor *czynnościowa pojemność zalegająca i pojedynczy oddech*	no correlation of reduced lung volumes to presence or absence of mild chieropathy *brak korelacji pomiędzy obniżoną objetością płuc a obecnością lub brakiem łagodnej chieropatii*
Makkar et al./*i wsp.* [8]	50	–	spirometry *spirometria*	reduced FEV_1, FVC, PEFR, MEF 75%, MEF 25% suggestive of a dominant restrictive and an obstructive pattern *obniżona FEV1, FVC,PEFR, MEF75%, MEF25% sugerujące dominujace zaburzenia restrykcyjne i obturacyjne*	diabetic patients with complications particularly peripheral neuropathy and nephropathy had significantly lower FEV_1, FVC and PEFR *pacjenci z cukrzycą powikłaną szczególnie obwodową neuropatią i nefropatią wykazują istotnie niższe FEV1, FVC and PEFR*
Schnack et al./*i wsp.* [9]	39	44	spirometry and whole body plethysmography *spirometria i pletyzmografia całego ciała*	TLC, FEV_1, Vital capacity and DL(CO) were reduced with a slight increase in airway resistance *TCL,FEV1, pojemność życiowa i DL(CO) były obniżone z niewielkich wzrostem oporności dróg oddechowych*	TLC, FEV_1, and Vital capacity correlated negatively with HbA_1c. Significantly lower TLC was found in patients with microalbuminuria (n=18) *TLC, FEV1 i objetośc calkowita ujemnie korelowaly ze stężeniem HbA1c. Istotne obniżenie TLC występowało u pacjentów z mikroalbimunurią(n=18)*
Meo et al./*i wsp.* [10]	27	27	spirometry *spirometria*	decreased FEV_1, and FVC,no difference in forced expiratory ratio, peak expiratory flow *obniżone FEV, FVC*	years of disease showed a dose response effect on lung function *czas choroby wykazał wpływ dawki na funkcje płuc*
Boulbou et al./*i wsp.* [11]	16	22	spirometry and DL(CO) in sitting and supine position *spirometria i DL(CO) w pozycji siedzacej i leżącej*	reduced TLC and FEV_1/FVC ratio and lower variation in DL(CO) by changing posture from sitting to supine *obniżone TLC , współczynnik FEV1/ FVC i mniejsza zmienność w DL(CO) przy zmienie pozycji z siedzącej na leżącą*	E-selectin concentration in serum was elevated in diabetes and showed the maximum contribution to the variation in DL(CO) *stężenie E-selektyny w surowicy było podwyższone w cukrzycy i wykazalo istotny wpływ na zmianę w DL(CO)*

FVC – forced vital capacity / *objetość życiowa płuc*
FEV_1 – forced expiratory volume in the 1st second / *maksymalna pojemność wydychana w pierwszej sekundzie*
TLC – total lung capacity / *całkowita pojemnośc płuc*
PEFR – peak expiratory flow rate / *szczytowy przepływ wydechowy*
DL(CO) – diffusion lung capacity for carbon monoxide / *pojemność dyfuzji płuc dla dwutlenku węgla*

Multiple determinants of pulmonary function abnormalities have been described in type 1 DM. These include poor metabolic control, presence of late diabetic complications, microalbuminuria and serum E-Selectin concentrations [2, 4, 8, 9]. The duration of diabetes had a dose response effect on lung function in the study by Meo et al. but had no effect on the reduced FVC in type 1 diabetes patients as reported by Primhak et al. [6, 10]. Presence or absence of mild cheiropathy has no effect on reduced lung volumes in type 1 DM patients [7]. However, in our study, neither poor metabolic control (as represented by the HbA_1c) nor the duration of diabetes had any impact on the FVC in the subset of patients with a restrictive ventilatory disturbance.

We did, however, detect a significant difference in the prevalence of a restrictive ventilatory disturbance depending on whether extreme stunting was present or not. As with any other chronic illnesses of catabolic nature, long term uncontrolled type 1 diabetes has been associated with stunting. Indeed, as already stated, nearly half of the children in our series were stunted and a quarter or so were extremely stunted. Uncontrolled diabetes leading to stunting may affect the growth and development of internal

organs including the lungs and may thus affect the normal accrual of lung function in childhood. To our knowledge ours is the first study to demonstrate the effect of stunting due to type 1 DM on pulmonary function.

To conclude, pulmonary function abnormalities detectable on spirometry are common in type 1 DM patients. A restrictive ventilatory disturbance appears to be the predominant pattern observed. Further extreme stunting as a result of childhood onset type 1 DM is associated with very high prevalence of restrictive ventilatory disturbances. This study is the first to document the adverse effects of stunting on pulmonary function, which in a childhood onset catabolic illness like type 1 DM leaves stunted children with reduced lung function for life. Prospective studies are required to study the longitudinal changes in lung function in both growing children and in adults with type 1 DM .

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