Type 1 Diabetes Duration Decreases Pulmonary Diffusing Capacity during Exercise

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Key Words

Altitude · Cardiac output · Exercise · Pulmonary diffusing capacity · Type 1 diabetes mellitus

Abstract

Background: Diabetes damages peripheral tissues; however, its effects on the lung are less known. Lung diffusing capacity (D_{LCO}) is influenced by alveolar-capillary membrane conductance (D_M) and pulmonary capillary blood volume (V_C), both of which are reduced in adults with type 1 diabetes (T1D). **Objective:** We sought to determine if diabetes duration affects D_{LCO} , D_M , V_C , and cardiac output (Q). **Methods:** 24 T1D patients (10.7–52.8 years) and 24 non-diabetic controls were recruited and had D_{LCO} , D_M , V_C , and Q measured at rest and during exercise (40, 70 and 90% VO_{2max}). **Results:** When stratified into two groups based on age (young, <20.6 years old), there were no significant differences in D_{LCO} , D_M , V_C , or Q (all of which were normalized to body surface area [BSA]) in the young group or in the old group. When stratified by diabetes duration (short duration, 0.33–8.9 years vs. long duration, 9.6–28 years), the T1D patients in the long duration group had lower D_{LCO}/BSA and D_M/BSA compared to the controls ($p < 0.05$). There were no differences in any of the variables in the short duration group. **Conclusions:** This study has shown that duration of diabetes is associated with decrements in diffusing capacity and its components.

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Introduction

The American Diabetes Association recommends that people with type 1 diabetes (T1D) engage in physical activity [1, 2]. It is unclear whether the effects on the lung limit the increasing number of people with diabetes who are participating in ‘adventure’ activities at moderate to high altitude [3]. Adults with T1D have pulmonary diffusion limitations [4, 5] that are particularly applicable when increased altitude reduces the alveolar-arterial gradient for oxygen transfer [6, 7]. Exercise exacerbates this challenge by increasing cardiac output and reducing the capillary transit times available for oxygen transfer in the lung [8]. Consequently, adventure activities at moderate to high altitude may result in more arterial hypoxemia, limiting the ability of individuals with diabetes to sustain vigorous activities at increased altitude.

The diffusing capacity of the lung (D_{LCO}) is determined by two components, the alveolar-capillary membrane diffusing capacity (D_M) and the pulmonary capillary blood volume (V_C) [9]. Diabetes thickens the pulmonary capillary basal lamina [10, 11] and increases endothelial permeability [12], reducing D_M . Niranjan et al. [13] showed that during exercise D_{LCO} was lower in healthy T1D adults and that the reduction in D_{LCO} was attributable to reduced D_M . They also showed that five years of intensive glycemic control prevented further de-

terioration of D_{LCO} . It is unclear whether adolescents with diabetes have the same impairment in pulmonary diffusion as adults. Van Gent et al. [14] found that D_{LCO}/V_C was not different from age-dependent norms in 27 children with T1D. In contrast, Cazzato et al. [15] found a lower D_{LCO} in children with T1D than in their age-matched controls but found no correlation with diabetes duration or HbA1c. However, Villa et al. [16] found that D_{LCO} was reduced in adolescents with diabetes and that D_{LCO} was inversely associated with HbA1c. These data suggest that age, magnitude or duration of hyperglycemia impairs pulmonary diffusion by altering the alveolar capillary membrane, but these changes to the diabetic lung are preventable.

Studies in diabetic adults suggest that reduced V_C [13, 17] causes reduced D_{LCO} . V_C is determined by the number of pulmonary capillaries in contact with ventilated alveoli. During exercise, lung volumes and pulmonary blood flow increase, causing an increase in D_{LCO} . Exercise is needed to evaluate V_C because only a small percentage of the pulmonary vasculature is used at rest; therefore, resting measures do not adequately assess microvascular reserve. An attenuated increase in cardiac output during exercise is well described in T1D [13, 18], and could reduce V_C by limiting recruitment and distension of pulmonary vessels [19–22]. Furthermore, microangiopathy in the lung in T1D patients may impair pulmonary vascular recruitment and distension by not allowing the normal increase in V_C [5].

The purpose of this study was to compare resting and exercising D_{LCO} , D_M and V_C , in children and adults with and without T1D at 7,000 ft (2,130 meters, barometric pressure ~600 mm Hg) to examine the effect of age and duration of disease on D_{LCO} and its components. We tested two hypotheses. The first was that older people with T1D would have a lower D_{LCO} compared to controls, but younger people with T1D would not. The second hypothesis was that subjects with a longer duration of diabetes (independent of age) would have a lower D_{LCO} compared to controls.

Methods

Subjects

Twenty-four individuals with T1D and 24 non-diabetic controls matched for age, self-reported fitness history and gender participated in this study. The subjects were aged 11–53 years, were non-smoking and showed no evidence of cardiovascular disease (Bruce protocol), microvascular impairment (proteinuria or retinopathy) or autonomic dysfunction. Three T1D participants were

Table 1. Subject characteristics

	Diabetics (n = 24)	Controls (n = 24)	p value
Age, years	23.8±12.2	24.2±12.9	0.238
Male gender, %	45.8	45.8	NA
Height, cm	166.6±14.7	166.8±12.2	0.936
Weight, kg	64.1±18.5	65.4±20.2	0.593
BMI	22.5±3.3	23.0±4.3	0.482
Body fat, %	23.8±7.4	22.9±7.0	0.463
Activity level, h/week	5.0±2.8	6.0±3.7	0.139
Diabetes duration, years	9.8±7.8	–	–
HbA1c ^a	7.9±1.3	–	–
VO ₂ max, ml/kg/min	34.9±5.8	36.3±7.7	0.307
Max. heart rate, bpm	181±13.8	187.0±14.1	0.136
RER at max.	1.1±0.1	1.1±0.1	0.951
FVC, % predicted	100.4±12.1	104.9±11.3	0.146
FEV _{1.0} , % predicted	97.6±15.9	100.9±11.6	0.379

Data are means ± SD. ^a n = 18.

taking ACE inhibitors; however, no participants were hypertensive (>140/90 mm Hg). The protocol was reviewed and approved by the Northern Arizona University Institutional Review Board, and all subjects signed a written informed consent prior to the study. In addition, adolescents filled out a self-assessment for Tanner stage of maturity [23].

Procedure

The study required two visits to the lab. During the first visit, height, weight and body fat percentage were determined using a seven-site skinfold method [24] on adults, and a two-site skinfold method on adolescents [25]. Standard spirometry testing was performed using a Medical Graphics CPX/D (St. Paul, Minn., USA) metabolic cart. Peak oxygen uptake (VO₂peak) (ParvoMedics TrueOne 2400; Sandy, Utah, USA) was then determined on a stationary cycle ergometer (Corival Lode B.V., The Netherlands).

VO₂peak was assessed using an incremental protocol. Adolescents pedaled at 60–70 rpm at an initial workload of 25 watts for subjects <14 years old and 40 watts for those >14 years old. The workload was then increased by 15 watts each min until exhaustion. Adults cycled 70–80 rpm. Females started at a workload of 50 watts and males at 100 watts and the workload was increased by 50 watts and then 25 watts every 2 min until exhaustion to make the total exercise duration between 8 and 14 min. Since the test was performed on a cycle ergometer, the classification of VO₂peak was based on either: (1) an increase in VO₂ of <250 ml with an increase in workload or (2) 2 of the following 3 situations – respiratory exchange ratio >1.10, the subject's inability to maintain the pedal rate or a heart rate within 10 beats/min of age-predicted maximum.

During the second visit, cardiac output (Q), D_{LCO} and lung diffusing capacity for nitric oxide (D_{LNO}) were measured using a re-breathing method. Two maneuvers were performed at rest and during each of the three exercise workloads (40, 70 and 90% of VO₂peak) for the measurement of D_{LCO} and D_{LNO} , and the determination of D_M [26], while simultaneously measuring Q. Subjects

Table 2. Resting and exercise variables measured in diabetics and their matched controls

	% of VO ₂ max	D _{LCO} /BSA	D _M /BSA	V _C /BSA	Q/BSA
Diabetics					
At rest	15.6±3.1	12.9±2.5	18.1±5.4	56.7±70.9	3.1±0.6
Exercise intensity					
Low	43.4±3.9	15.7±2.7	20.8±3.6	64.2±40.2	5.9±1.3
Moderate	72.2±4.6	17.9±3.4	23.9±4.9	73.3±59.9	7.4±1.4
High	92.5±6.0	19.5±4.3	28.2±7.0	60.8±24.9	8.6±1.7
Controls					
At rest	15.7±4.1	13.4±2.2	18.4±4.8	56.9±30.2	3.2±0.8
Exercise intensity					
Low	43.3±5.9	16.3±3.5	21.4±5.3	68.8±30.8	6.2±1.4
Moderate	70.3±8.7	19.5±3.8	25.9±6.3	73.2±30.6	8.3±1.5
High	89.3±10.4	21.5±4.6	28.8±6.3	75.4±21.5	9.5±1.5
Data are means ± SD.					

rebreathed a gas mixture containing 0.6% C₂H₂, 0.28% C¹⁸O, 9% He, 36.1% O₂, and 40 ppm NO from a 5-liter anesthesia bag for 8 breaths. Breathing was set at a rate of 32 breaths/min using a metronome until the respiratory rate exceeded 32 breaths/min, at which point the metronome was set at the subject's preferred breathing rate. Gases were sampled with a Perkin Elmer MGA-1100 mass spectrometer (Wesley, Mass., USA) and Sievers 280i Nitric Oxide Analyzer (GE; Boulder, Colo., USA), and analyzed on a PC using custom software (KC Beck; Liberty, Utah, USA) for the measurement of D_{LCO}, D_{LNO} and Q. The bag volume corresponded to the subject's normal tidal volume plus 200 ml of the gas mixture. During rebreathing, D_{LCO}, D_{LNO} and Q were measured from the slope of the end-tidal exponential disappearance of C¹⁸O, NO and acetylene, respectively, with respect to He over time. These data were used to calculate the two components of D_{LCO}, D_M and V_C, using the Roughton and Forster [9] equation.

Statistical Analysis

Data are reported as mean ± SD. Statistical analyses were performed using SigmaStat 3.5 (Systat Software, Inc.; Point Richmond, Calif., USA). A two-way analysis of variance with repeated measures was used to determine differences in Q, D_{LCO}, D_M, and V_C (dependent variables) between the groups, exercise intensity and the interaction of group and condition (independent variables). The post-hoc test, Holm-Sidak, was used when appropriate. The results were considered statistically significant if $p < 0.05$.

Results

Subject testing starting in February 2011 and was completed in September 2012. The whole group subject characteristics are shown in table 1. The T1D and control groups were of similar age, height, weight, percent body fat, and activity level. There were no group differences in

VO₂peak, respiratory exchange ratio and heart rate at maximal exercise or pulmonary function.

D_{LCO}/body surface area (BSA), D_M/BSA, V_C/BSA, and Q/BSA were measured at rest, and low, moderate and high exercise intensities. D_{LCO}/BSA, D_M/BSA and Q/BSA increased with increased exercise intensity. D_{LCO}/BSA ($p = 0.167$), D_M/BSA ($p = 0.494$), V_C/BSA ($p = 0.569$), or Q/BSA ($p = 0.112$) were not different across the testing conditions (table 2). Relative exercise intensities were not different between the groups ($p = 0.390$).

The effect of age on D_{LCO} was determined by stratifying subjects around the median age (20.7 years) of the sample. The average age of the young and older groups was 15.3 ± 4.0 years and 32.3 ± 11.8 years, respectively ($p < 0.05$). In the young group, D_{LCO}/BSA, D_M/BSA and Q/BSA, but not V_C/BSA, increased with increasing exercise intensity. In the older group, D_{LCO}/BSA, D_M/BSA, V_C/BSA, and Q/BSA increased with increasing exercise intensity. There were no differences in D_{LCO}/BSA, D_M/BSA, V_C/BSA, and Q/BSA between the young and older T1D patients and their age-matched controls (table 3).

The sample was then stratified around the median duration of diabetes (9.3 years), and those above and below the median duration were compared against their assigned age- and sex-matched controls. In both groups, D_{LCO}/BSA, D_M/BSA and Q/BSA increased with increasing exercise intensity ($p < 0.05$). In the long-duration group, V_C/BSA increased with increasing exercise intensity ($p < 0.05$). There were no differences in D_{LCO}/BSA, D_M/BSA, V_C/BSA, and Q/BSA ($p = 0.328$, 0.155 , 0.601 , and 0.263 , respectively) for the short-duration T1D pa-

Table 3. Resting and exercise variables in diabetics and controls stratified by age

	D _{LCO} /BSA	D _M /BSA	V _C /BSA	Q/BSA
<i>Young</i>				
Diabetics				
At rest	13.1±3.2	17.2±6.1	81.8±105.9	3.3±0.6
Exercise intensity				
Low	15.7±3.5	20.9±4.6	61.4±29.0	6.1±1.2
Moderate	17.4±3.9	23.2±6.0	87.6±83.8	7.1±1.0
High	19.4±5.0	28.5±8.7	55.2±18.5	8.4±2.0
Controls				
At rest	13.7±1.9	19.5±5.0	64.1±40.2	3.3±0.6
Exercise intensity				
Low	15.6±3.8	20.2±4.6	71.8±38.5	5.9±1.3
Moderate	19.6±3.9	25.8±5.3	72.4±38.6	8.5±1.6
High	20.9±4.9	27.9±6.2	71.1±25.4	9.4±1.5
<i>Older</i>				
Diabetics				
At rest	12.9±2.0	18.7±4.9	37.9±10.3	2.9±0.6
Exercise intensity				
Low	15.7±1.8	20.7±2.6	67.1±50.2	5.8±1.3
Moderate	18.3±3.0	24.5±3.7	60.2±19.8	7.7±1.7
High	19.7±3.7	28.0±5.2	66.4±29.8	8.8±1.3
Controls				
At rest	13.0±2.5	17.5±4.8	50.9±18.3	3.1±0.9
Exercise intensity				
Low	17.0±3.3	22.5±6.0	65.9±22.1	6.4±1.4
Moderate	19.5±3.9	26.1±7.4	73.9±23.0	8.2±1.3
High	22.0±4.4	29.6±6.5	78.9±17.9	9.5±1.6

Data are means ± SD.

tients (4.0 ± 2.8 years) versus the non-diabetic controls. Similarly, there were no differences in V_C/BSA and Q/BSA ($p = 0.115$ and 0.234 , respectively) between the long-duration T1D patients (15.7 ± 6.6 years) versus the matched controls. However, long-duration T1D patients had lower D_{LCO}/BSA ($p = 0.014$) and D_M values ($p = 0.033$) than the matched controls (fig. 1, 2).

Discussion

Our study of non-smoking adolescents and adults found that resting and peak exercise D_{LCO} were not significantly different between controls versus T1D patients. Contrary to our hypothesis, neither younger nor older patients were different from their age- and sex-matched controls. However, when the participants were stratified by diabetes duration, we found that people with longer T1D diagnoses (>10 years) had reduced D_{LCO} relative to the controls, and this difference was exacerbated during high-intensity exercise. Simultaneous measurements of

D_{LCO} and D_{LNO} in our study showed that the reduction in D_{LCO} was due to a lower D_M , but that V_C was not significantly affected. None of the participants had evidence of microangiopathy, and there was no significant relationship between D_{LCO} and HbA1c levels. These findings suggest that diabetes-specific impairment of pulmonary diffusion is a progressive process.

Our finding that age-matched D_{LCO} did not differ between normal and T1D subjects does not agree with some previous reports of impaired resting pulmonary diffusing capacity in adults [4, 17, 27–29] and adolescents [14, 16, 30] with T1D. However, some [17], but not all [16] of these earlier studies also reported abnormal pulmonary function in their subjects, whereas our T1D cohort had normal pulmonary function (spirometry). Normal lung volumes and ventilatory flows in our diabetic cohort may have allowed them to transfer CO more effectively, whereas the pathology in the previous studies' cohorts [14, 15, 17, 30] did not. Nonetheless, a study of children with normal spirometry tests has also reported impaired D_{LCO} [16].

Fig. 1. D_{LCO}/BSA at rest and low, moderate and high exercise intensities for the long-duration diabetics and their matched controls (**a**) and for the short-duration diabetics and their matched controls (**b**). * $p < 0.05$, a difference between diabetics and controls. † $p < 0.05$, different from the rest. ‡ $p < 0.05$, different from low-intensity exercise. # $p < 0.05$, different from moderate-intensity exercise.

Fig. 2. D_M/BSA at rest and low, moderate and high exercise intensities for the long-duration diabetics and their matched controls (**a**) and for the short-duration diabetics and their matched controls (**b**). * $p < 0.05$, a difference between diabetics and controls. † $p < 0.05$, different from the rest. ‡ $p < 0.05$, different from low-intensity exercise. # $p < 0.05$, different from moderate-intensity exercise.

Another possibility is that differences in global diabetes control or behavior between our cohort and previous cohorts may have contributed to differences in D_{LCO} observations. Several studies reporting lower D_{LCO} in T1D patients have included nephropathic [29, 31], neuropathic [29] and retinopathic [28, 32] patients. Other cohorts have been composed of patients with higher mean HbA1c values than the present study [30]. Two studies stratified participants with T1D into good and poor glycemic control [16, 33] and found that pulmonary diffusion was impaired in those with poor control, but not in those with

HbA1c <7% (53 mmol). None of the participants in this study had clinically evident microvascular abnormalities, and the HbA1c levels were, in relation to previous studies, lower. Considering the association between glycemic control and microvascular complications [34], group differences in D_{LCO} might have been even more evident if our cohort had worse metabolic control. The average HbA1c value in our subjects was 7.9; while among the studies showing differences in D_{LCO} between diabetics and controls [13, 15, 16, 29, 30, 32, 33, 35], only one study had HbA1c values lower than ours [15], the rest had an

average HbA1c level in their subjects of 8.98%. Yet another possibility for the lack of difference within the age groups may be the wide range of durations. In the diabetic adolescents, the disease duration ranged from 0.33 to 14 years, while in the adults, it ranged from 6.5 to 28 years.

Our finding that diabetes duration was associated with reduced pulmonary diffusion expands on the findings of Asanuma et al. [4] who found that the decrease in D_{LCO} was correlated with diabetes duration in adults with T1D. However, retinopathy was also correlated with diabetes duration in their cohort, raising the possibility that microangiopathy, which worsened with diabetes duration, explained the reduction in D_{LCO} rather than uncomplicated diabetes duration. Villa et al. [16] found that glycemic control, but not diabetes duration reduced D_{LCO} in a small cohort of children; however, their cohort had a significantly smaller range of diabetes duration than the present study. In the present study, D_{LCO} was lower in a cohort free of microvascular complications with relatively long diabetes duration (14.8 ± 7.3 vs. 5.0 ± 4.4 years), which is considerably longer than that of previous studies.

The most novel aspect of our study design was our measurement of D_{LCO} during peak exercise. Alveolar ventilation and pulmonary capillary perfusion are maximized during peak exercise and the demand for oxygen transfer is greatest in this state. Therefore small, often insignificant differences in resting D_{LCO} can increase when these systems are stressed. Studies in adults have confirmed greater impairment in pulmonary diffusion in the exercise versus the resting state that has been attributed to reduced D_M [33], V_C [17] or both [13]. However, these findings are limited to adults with poor glycemic control [13, 33]. The present study showed a significant reduction in D_{LCO} and D_M , but not V_C , during exercise in patients (young and older) with a long duration of diabetes, suggesting that diabetes affects the pulmonary capillary membrane in a manner independent of age. The lack of difference in V_C may reflect the fact that cardiac output was not lower in our diabetic cohort, as seen in other studies [13, 33]. Vracko et al. [10] and Weynand et al. [11] described thickened alveolar and capillary basal laminae in post-mortem diabetic lungs, which also occurred in the renal and muscle capillaries. It is generally believed that these permanent changes in basal membrane protein structure accumulate over time [36]. Our data in the diabetic lung support this hypothesis.

One unexpected finding of this study was a reduction in V_C during high-intensity exercise in the young subjects

with diabetes. We believe the drop to be partly due to the innate variability of the measurement, but it could also be due to the subjects exhibiting a mild hypoxic response to the testing being performed at moderate altitude (~2,100 meters). Our changes from rest to moderate exercise are of nearly identical magnitude to those described previously [20, 37]. We are not sure why we did not see increases from moderate- to high-intensity exercise, but the possibility of hypoxic vasoconstriction from exercising at moderate altitude may be one possible explanation to why further increases in V_C at the highest exercise intensities were not seen [38].

An unusual aspect of this study is that it was conducted at moderate altitude (2,100 m). The lower inspired PO_2 found at moderate altitude impairs oxygen diffusion by reducing the alveolar-arterial O_2 gradient [39]. Chance et al. [40] have suggested that the non-symptomatic reduction in D_{LCO} during sea-level rest might become functionally limiting when diabetic individuals exercise at increased altitude. However, we found that our diabetic cohort had similar decreases in D_{LCO} at altitude to those who have performed similar studies at or near sea level [33]. Moreover, any reductions in D_{LCO} were not sufficient to result in a difference in S_aO_2 (data not shown) or exercise capacity between the groups. This may reflect the relatively minor hypoxia (P_{AO_2} ~65–75 mm Hg) at this altitude and/or the high level of metabolic control and healthy lifestyle of our participants.

This study found that D_{LCO} was significantly affected in people with longer diabetes duration (who had reduced D_{LCO}), which was exacerbated by high-intensity exercise. The lower D_{LCO} was associated with a decreased D_M , but not V_C , suggesting that the 'T1D effect' related to changes in the alveolar capillary membrane. Despite the fact that the experiments were conducted at moderate altitude, the differences in pulmonary diffusion did not result in a lower arterial saturation during exercise in people with long-duration diabetes. Our interpretation of these findings is that pulmonary diffusion, though impaired, does not limit the aerobic capacity in people with well-controlled T1D.

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