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Diabetes mellitus and ventilatory capacity: a five year follow-up study

P. Lange, S. Groth, J. Mortensen, M. Appleyard, J. Nyboe, P. Schnohr, G. Jensen

Diabetes mellitus and ventilatory capacity: a five year follow-up study. P. Lange, S. Groth, J. Mortensen, M. Appleyard, J. Nyboe, P. Schnohr, G. Jensen.
ABSTRACT: During a five year observation period, declines of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were investigated in 200 subjects with diabetes mellitus (DM), 126 subjects who developed DM during that period and 9,051 nondiabetic subjects. After statistical adjustment for age, sex, height, and tobacco consumption we found that the subjects who developed DM during the observation period had the steepest declines of ventilatory function. Their annual declines of FVC (and FEV_1) were on average 29 ml (and 25 ml) greater than the declines observed among the nondiabetic subjects. The subjects who had DM during the whole observation period experienced a decline of ventilatory function which was not significantly greater than the decline among the nondiabetic subjects. Our results suggest that DM, at its onset, is associated with a significantly accelerated decline of ventilatory function. If DM has been present for some years, its impact on the decline of ventilatory function is small.
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During the last decade it has been repeatedly observed that insulin-dependent diabetes mellitus (IDDM) is associated with a slight impairment of lung function [1–7]. Recently, we have found that a slight reduction of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) may be present in all age-groups among subjects with diabetes mellitus (DM), both IDDM and non-insulin-dependent diabetes mellitus (NIDDM) [8]. In addition, we found a dose-response relationship between the level of plasma glucose in subjects without known DM and the impairment of ventilatory function. The subjects with most pronounced hyperglycaemia had the most pronounced reduction of ventilatory function. Our results suggested that diabetes-related reduction of ventilatory function might be present in patients with newly diagnosed DM and even among subjects with pre-diabetes.

To investigate whether the onset of DM is associated with impairment of ventilatory capacity we analysed the decline of FEV_1 and FVC during a period of 5 yrs in subjects who developed DM during that period, subjects with DM throughout the period, and nondiabetic subjects.

Subjects and methods

The subjects included in the present analysis were, in 1976–1978, enrolled in The Copenhagen City Heart Study, which is a prospective cardiovascular epidemiological study of an age-stratified random sample of the general population. Selection procedure of the study sample has been described in a previous paper [8] and is given in detail elsewhere [9, 10]. The first examination took place from 1976–1978 and the second from 1981–1983. A total of 11,135 subjects attended both examinations. For each participant the interval between the examinations was as close as possible to 5 yrs.

At both examinations, the recordings of FEV_1 and FVC were made on the same electronic spirometer (Monaghan N 403, Littleton, Colorado), which was calibrated daily. As a criterion for the correct performance at least two measurements within 5% of each other had to be produced. The largest volume was used in the analysis.

The diagnosis of DM was based on the questionnaire. Plasma glucose was measured with a hexokinase method utilizing non-fasting blood samples from a cubital vein.

The subjects who could not perform a correct spirometry, those who were uncertain whether they had DM and those with incomplete data required for the analysis were excluded. The remaining 9,377 subjects were classified into the following groups:
Known DM (KDM): 200 subjects who were either reported to have DM or had a plasma glucose higher than 11.1 $mmol \cdot l^{-1}$ at the first examination.
New DM (NDM): 126 subjects who, at the first examination, were reported not to have DM and had a plasma glucose lower than 11.1 $mmol \cdot l^{-1}$ and who at the second examination were reported to have DM or had a plasma glucose higher than 11.1 $mmol \cdot l^{-1}$.

Controls: 9,051 subjects who at both examinations were reported not to have DM and had plasma glucose lower than 11.1 mmol·l^{-1}.

There were too few subjects with IDDM to analyse this type of DM separately.

A few weeks after each examination, all subjects who were unaware of having DM, but had plasma glucose higher than 8.5 mmol·l^{-1} for women and 9.0 mmol·l^{-1} for men were advised to contact their general practitioner, who was also notified directly by us.

Statistical analysis

For each individual, the difference between FEV_1 (and FVC) at first and second investigation was divided by the actual length of the observation period to obtain an estimate of the annual FEV_1 change (ΔFEV_1) and the annual FVC change (ΔFVC). To assess the association between ΔFEV_1 (and ΔFVC) and KDM and NDM and simultaneously adjust for other possible confounding variables, multiple linear regression was used. The regression was performed on all 9,377 evaluable subjects and included ΔFEV_1 or ΔFVC (in ml·yr^{-1}) as the dependent variable and KDM (KDM=1, NDM or control=0) and NDM (NDM=1, KDM or control=0) as the independent variables of interest. As the other independent variables we included age (yrs), height (cm), change in body weight between the two examinations (kg) and average daily tobacco consumption during the follow-up (g·day^{-1}). Initially, sex (women=0, men=1) was also included as an independent variable but as this variable

Table 1. – General characteristics of the control subjects, subjects with known diabetes mellitus (DM) (KDM), and subjects with new DM (NDM)

	Women			Men		
	Controls n=5,206	KDM n=67	NDM n=49	Controls n=3,845	KDM n=133	NDM n=77
Age yr	51.8 (11)	55.6 (10)	58.8 (9)	51.1 (12)	57.0 (9)	53.9 (11)
Glucose at 1 exam mmol·l^{-1}	6.2 (1)	12.5 (5)	7.9 (2)	6.5 (1)	13.4 (5)	7.7 (1)
Glucose at 2 exam mmol·l^{-1}	5.9 (1)	11.5 (6)	12.2 (5)	6.2 (1.0)	11.3 (5)	12.8 (5)
FEV_1 *l*	2.29 (0.6)	2.02 (0.5)	2.00 (0.6)	3.17 (0.8)	2.67 (0.7)	2.80 (0.7)
FEV_1 % pred	95 (18)	89 (16)	92 (17)	96 (19)	87 (20)	89 (17)
FVC *l*	2.84 (0.6)	2.54 (0.6)	2.47 (0.6)	3.98 (0.9)	3.44 (0.8)	3.53 (0.8)
FVC % pred	99 (17)	93 (16)	94 (17)	98 (17)	91 (18)	93 (15)
Change in body weight between the exams kg	0.8 (6)	-2.5 (7)	-2.5 (7)	0.9 (5)	-1.9 (6)	-1.5 (8)

Mean values with SD in parentheses. 1 exam: first examination; 2 exam: second examination; pred: predicted values. Predicted values were obtained by estimating the regression of FEV_1 and FVC on age and height among asymptomatic nonsmokers from The Copenhagen City Heart Study [11]. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. The change in body weight was calculated as the weight at second examination minus weight at first examination.

Table 2. – Prevalence of nonsmokers among the subjects in different DM groups

	Women			Men		
	Controls n=5,206	KDM n=67	NDM n=49	Controls n=3,845	KDM n=133	NDM n=77
Nonsmokers % at 1 examn	44	51	51	32	38	46
Nonsmokers % at 2 examn	48	53	59	37	44	47

DM: diabetes mellitus; KDM: known DM; NDM: new DM.

did not reach significance it was excluded from the final model. Finally, it was decided not to include the initial level of the ventilatory function in the regression model, as has recently been suggested by VOLLMER [12]. The final regression model was:

ΔFEV_1 (or ΔFVC) = $k_0 + k_1 \cdot age + k_2 \cdot height + k_3 \cdot change$ in body weight + $k_4 \cdot$tobacco consumption + $k_5 \cdot KDM + k_6 \cdot NDM$

The k's are regression coefficients. The fit of the model was tested by plotting the residuals against the predicted values of ΔFEV_1 and ΔFVC and against each of the independent variables. First order interaction terms were included to investigate whether the fit of the model could be significantly improved.

Results

Table 1 shows the general characteristics of the subjects including mean values of age, ventilatory function at the time of enrolment, mean plasma glucose at both examinations and the difference between the body weight at first and second examination. At the first examination, the mean FEV_1 and FVC of the KDM group was significantly lower than that of the control group, but the mean FEV_1 and FVC in the NDM were also slightly reduced. On average, the subjects who developed DM and those with DM already present at first examination experienced a weight loss between the examinations, while the non-diabetic subjects experienced a gain in body weight.

Table 2 shows the changes in smoking habits between the first and second examination. In all groups there was a slight tendency to quit smoking. This trend was most pronounced among women in the NDM group.

In both sexes, the unadjusted mean values of ΔFEV_1 and ΔFVC were higher in the NDM group compared to the values in the KDM group and in the control group (table 3).

The results of multiple regression analyses are given in table 4. There was a significant association between ΔFEV_1 and ΔFVC and presence of NDM. The regression coefficient for NDM indicates that, on average, the subjects in the NDM group had a 25 ml (and 29 ml) greater decline of FEV_1 (and FVC) than the control

Table 3. – Unadjusted annual decline of FEV_1 and FVC according to sex and diabetes

Decline of ventilatory function	Women			Men		
	Controls n=5,206	KDM n=67	NDM n=49	Controls n=3,845	KDM n=133	NDM n=77
ΔFEV_1 ml·yr^{-1}	26 (1)	23 (10)	54 (14)	35 (2)	42 (12)	57 (12)
ΔFVC ml·yr^{-1}	29 (2)	20 (13)	64 (15)	42 (3)	61 (13)	64 (13)

Mean values with SE in parentheses. ΔFEV_1: mean annual decline in forced expiratory volume in one second; ΔFVC: mean annual decline in forced vital capacity. For further abbreviations see legend to table 2.

Table 4. – Regression analysis of ΔFVC and ΔFEV_1 of all subjects on age, height, change in body weight, tobacco consumption and diabetes mellitus

Independent variable	ΔFEV_1 ml·yr^{-1}			ΔFVC ml·yr^{-1}		
	Regression coefficient	SE	p	Regression coefficient	SE	p
Intercept	-134.7	23.9	<0.001	-175.9	28.2	<0.001
Age yr	1.2	0.1	<0.001	1.3	0.1	<0.001
Height cm	0.6	0.1	<0.001	0.8	0.2	<0.001
Change in body weight kg	1.5	0.2	<0.001	1.9	0.2	<0.001
Tobacco consumption g·day^{-1}	0.8	0.1	<0.001	0.6	0.1	<0.001
KDM, 1=KDM 0=no KDM	0.6	8.0	NS	8.3	9.3	NS
NDM, 1=NDM 0=no NDM	24.9	10.0	<0.02	28.8	11.9	<0.02

NS: not significant. For further abbreviations see tables 2 and 3.

subjects. There was no significant association between the presence of KDM and the decline of FEV_1 and FVC (table 4).

The established associations between ΔFEV_1 (and ΔFVC) and age, height, and tobacco consumption were also found in this study (table 4). An increase in body weight was also significantly associated with a slightly greater decline in ventilatory function (table 4).

There were no significant interactions between the effects of the independent variables.

Discussion

This study shows an association between newly developed DM and decline of ventilatory capacity. The involvement of the vascular and neural system in DM is profound and has been subject to extensive study, but so far little is known about the effects of DM on the lung. Pathoanatomical studies of the lungs from diabetic subjects have presented evidence for changes in basal laminae of alveolar epithelium and capillaries [13]. Slight abnormalities in the carbon monoxide transfer factor and in the elastic properties of the lung have been reported in some studies [1–7] but not all [14–15]. In a few studies, a slight reduction of static and dynamic lung volumes has been observed in subjects with IDDM [3, 4, 15]. However, the abnormalities observed have been small, which is in agreement with clinical experience indicating that apart from the rare appearance of adult respiratory distress syndrome in severe diabetic ketoacidosis [16], lung involvement is generally not a clinically important feature of DM.

Within the last few years, observations of morphological and biochemical abnormalities have been reported in the lungs of rats with streptozotocin-induced DM [17–19]. OFULUE and THURLBECK [19] have shown that untreated diabetic rats have a significantly decreased degradation of lung connective tissue compared to normal rats. As the diabetic rats have a synthesis of lung connective tissue no different from the nondiabetics rats, the decreased degradation might result in an accumulation of connective tissue similar to that occurring in various organs of patients with DM [20–23]. This accumulation might be due to non-enzymatic glycosylation of proteins, a process which has been suggested as a common link between hyperglycaemia and the development of long-term diabetic complications [23, 24]. Glycosylation of collagen results in irreversible collagen cross-linking and accumulation of collagen, as the cross-linked end-product is less susceptible to proteolysis than native collagen. KOHN and SCHNIDER [23] have suggested that if there were a limited number of sites in collagen available for glycosylation, it could be expected that particularly high glycosylation activity was present in the early stages of DM. Control of DM may play an important role in lung connective tissue metabolism as shown by OFULUE and THURLBECK [19]. In their study on diabetic rats, they showed that the rats treated with insulin had a degradation of connective tissue not significantly different from that of nondiabetic rats [19]. If accumulation of cross-linked collagen also occurs in the lungs of patients with untreated DM, functional changes resembling mild interstitial fibrosis may follow. This may also explain why we found the most pronounced acceleration of the ventilatory function decline in subjects with newly developed DM. In more advanced DM, the glycosylation of collagen tends to decelerate eventually reaching a new equilibrium at a lower turn-over rate of collagen [23]. Thus, if the cross-linking of collagen is a non-progressive or a very slowly progressive process, there need not be a distinct association between ventilatory function impairment and duration of DM [8, 15]. In fact, our results suggest that once DM is known and controlled, the decline of ventilatory function is not significantly greater than that of nondiabetic subjects (table 4). To elucidate this hypothesis further long-term follow-up studies of patients with newly diagnosed DM, or subjects with impaired glucose tolerance who have not yet developed DM are needed.

This study shows that subjects with newly developed DM have almost twice as high a decline of ventilatory function as the nondiabetic subjects. Subjects who have had DM for some years experience a decline of ventilatory function which is not significantly greater than the decline observed among nondiabetic subjects. It is hypothesized that the excessive decline of ventilatory function in subjects with newly developed DM may be due to cross-linking of pulmonary collagen.

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Le diabète sucré et la capacité ventilatoire: un suivi pendant 5 ans. P. Lange, S. Groth, J. Mortensen, M. Appleyard, J. Nyboe, P. Schnohr, G. Jensen.

RÉSUMÉ: Pendant une période d'observation de 5 ans, l'on a étudié le déclin de la capacité vitale forcée (FVC) et du volume expiratoire maximal seconde (VEMS) chez 200 sujets atteints de diabète sucré (DM), 126 sujets qui ont développé un diabète au cours de cette période et 9051 sujets non diabétiques. Après ajustement statistique pour l'âge, le sexe, la taille, la fonction pulmonaire initiale et la consommation de tabac, nous avons trouvé que les sujets qui ont développé un diabète au cours de la période d'observation avaient le déclin le plus marqué de la fonction ventilatoire. Leur diminution annuelle de capacité vitale forcée et du VEMS furent en moyenne de 29 et de 25 ml supérieurs au déclin observé chez les sujets non diabétiques. Les sujets qui ont eu du diabète pendant toute le période d'observation n'ont pas un déclin fonctionnel ventilatoire significativement plus élevé que celui des sujets non diabétiques. Nos résultats suggèrent que le diabète sucré, à sa période initiale, est associé à une accélération significative du déclin de la fonction ventilatoire. Si le diabète sucré existe depuis plusieurs années, son impact sur le déclin de la fonction ventilatoire est limité.

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