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Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study

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ABSTRACT: To assess possible associations between diabetes mellitus (DM), plasma glucose, forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), we analysed the results from a cross-sectional study of 11,763 subjects. The subjects were 20 yrs of age or older and were representative of the population of Copenhagen City. Two hundred and eighty four of the participants had DM as assessed by questionnaire. One hundred and seven subjects who did not report having DM had a plasma concentration of glucose higher than or equal to 11.1 mmol·l^{-1}. In all age groups of diabetic subjects there was a slight impairment of lung function. It was more prominent in diabetic subjects treated with insulin than in subjects treated with oral hypoglycaemic agents and/or diet. Even in subjects without known DM, there was a significant association between reduction in lung function and raised plasma glucose concentration. On average, FVC (and FEV_1) was reduced by 334 ml (and 239 ml) in diabetic subjects treated with insulin, and by 184 ml (and 117 ml) in diabetic subjects treated with hypoglycaemic agents and/or diet compared to control subjects.
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During the last decade several studies of lung function in patients with insulin-dependent diabetes mellitus (IDDM) have been published [1–7]. Some investigators have found reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) among diabetic patients compared to normal individuals [4, 5], while others have been unable to demonstrate any changes in these lung function indices in diabetic subjects [1–3, 6, 7]. An obvious reason for this discrepancy might be that only small numbers of diabetic subjects have been studied.

To examine the possible impact of diabetes mellitus (DM) and plasma glucose on FVC and FEV_1 we have studied a population sample of 11,763 subjects.

Subjects and Methods

The subjects included in this analysis took part in the second examination of the Copenhagen City Heart Study, which is a prospective cardiovascular epidemiological study initiated in 1976. An age-stratified random sample of 18, 125 individuals with the majority of the subjects being between 40–70 yrs of age were invited by letter to attend this examination. From 1981 to 1983, 12,698 responders were examined. Details on the selection procedure of the study sample and a description of the non-responders have been given elsewhere [8, 9] together with an outline of the questionnaire and the complete examination programme.

The diagnosis of DM was based on the questionnaire. The diabetic subjects were subdivided according to the treatment of DM into: subjects treated with insulin (DM 1); and subjects treated with oral hypoglycaemic agents and/or diet (DM 2). The subjects who were uncertain whether they had DM were excluded together with subjects with incomplete data required for the analysis.

Plasma glucose was measured with a hexokinase method utilizing non-fasting blood samples from a cubital vein. All subjects were subdivided into the following groups: subjects with plasma glucose lower than 7.8 mmol·l^{-1} (GLU 0); subjects with plasma glucose higher than or equal to 7.8 mmol·l^{-1} but lower than 11.1 mmol·l^{-1} (GLU 1); and subjects with plasma glucose higher than or equal to 11.1 mmol·l^{-1} (GLU 2).

Table 1. – Distribution of the participants according to the presence of diabetes mellitus and plasma concentrations of glucose

	no DM	DM 1	DM 2
GLU 0	10,654	10	65
GLU 1	718	13	66
GLU 2	107	45	85

DM: diabetes mellitus; no DM: subjects who reported that they had no diabetes mellitus; DM 1: subjects treated with insulin; DM 2: subjects treated with oral hypoglycaemic agents and/or diet; GLU 0: subjects with plasma glucose lower than 7.8 mmol·l^{-1}; GLU 1: subjects with plasma glucose higher than or equal to 7.8 mmol·l^{-1} but lower than 11.1 mmol·l^{-1}; GLU 2: subjects with plasma glucose higher than or equal to 11.1 mmol·l^{-1}.

were employed on the non-adjusted lung function values. The regression equations included age (yrs), sex, height (cm), body mass index (BMI) (kg·m^{-2}), tobacco consumption (g·day^{-1}), DM (DM 1 and DM 2) and in some instances plasma glucose (GLU 1 and GLU 2) as the independent variables. The regression model was:

$$FEV_1 \text{ or } FVC=K_0+K_1\cdot age+K_2\cdot sex +K_3\cdot height+K_4\cdot BMI+K_5\cdot tobacco\ consumption+ K_6\cdot DM\ 1+K_7\cdot DM\ 2+K_8\cdot GLU\ 1+K_9\cdot GLU\ 2$$

K is a regression coefficient. Sex, DM and plasma glucose were included as binary variables: sex (1=male, 0=female); DM 1 (1=DM 1, 0=no DM); DM 2 (1=DM 2, 0=no DM); GLU 1 (1=GLU 1, 0=GLU 0); GLU 2 (1=GLU 2, 0=GLU 0).

Table 2. – General characteristics and the average height standardized lung function of the participants according to sex and presence of diabetes

	Men			Women		
	Normals n=5,107	DM 1 n=37	DM 2 n=139	Normals n=6,372	DM 1 n=31	DM 2 n=77
Age yrs	55.3	57.1	62.3	56.0	56.8	63.4
Height cm	174	173	172	161	163	159
BMI kg·m^{-2}	25.9	23.7	27.8	24.8	24.4	29.4
Glucose mmol·l^{-1}	6.4	14.4	10.8	5.9	14.4	10.8
FEV_1 *l*	2.96	2.71	2.57	2.18	1.94	1.90
FVC *l*	3.72	3.37	3.22	2.71	2.41	2.38
never-smokers %	12	9	10	29	23	31
ex-smokers %	24	37	37	18	32	25
smokers %	64	54	53	53	45	44

Normals: subjects who reported that they had no diabetes mellitus; DM 1: subjects treated with insulin; DM 2: subjects treated with oral hypoglycaemic agents and/or diet; BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Pulmonary function

All recordings were made on an electronic spirometer (Monaghan N 403, Littleton, Colorado), which was calibrated daily against a Godard spirometer. To determine FEV_1 and FVC, the subjects inhaled to total lung capacity before beginning an abrupt forced expiration and without hesitation. Maximum effort was to be exerted throughout the expiration which was to last at least 4 s. No less than three acceptable measurements were obtained. The largest volume was used. As a criterion for correct performance, a reproducibility of measurements within 95% was used. A sample of 142 subjects who could not perform a correct spirometry was excluded, leaving 11,763 in the study group.

Statistical analysis

The FEV_1 and FVC were adjusted separately to the height of a typical male or female subject [10]. The height-adjusted spirometric values of subjects in the two DM-categories were compared to the values of non-diabetic subjects. A series of multiple linear regressions

Possible interactions between DM and the other independent variables were investigated by expanding the regression model with interaction terms.

Results

The relation between the presence of DM as assessed by the questionnaire and the measurements of plasma glucose is given in table 1. According to measurements of plasma glucose, one hundred and seven subjects had DM without knowing it.

In table 2, the general characteristics and the lung function data of the participants are given separately for men and women. On average, subjects in the DM 2 group were older and more obese than the remaining subjects. There were slight differences in the smoking habits between the groups with a higher prevalence of ex-smokers and a lower prevalence of smokers among diabetic subjects than among control subjects.

Tables 3 and 4 present the height-adjusted values of FEV_1 and FVC according to sex, age, smoking habits, and presence and type of DM. In almost all of the subgroups, the diabetic subjects had slightly smaller

Table 3. – Height-standardized FEV_1 (*l*) according to sex, age, smoking and diabetes mellitus

Age	Men			Women		
yrs	Normals	DM 1	DM 2	Normals	DM 1	DM 2
20–49	n=1,574	n=7	n=21	n=1,10	n=6	n=7
smk-	3.77	3.62	3.54	2.75	2.35	2.37
smk+	3.50	2.84	2.86	2.59	2.45	2.70
50–59	n=1,77	n=15	n=21	n=1,843	n=12	n=15
smk-	3.11	2.64	2.50	2.31	1.85	2.00
smk+	2.83	2.75	2.65	2.10	1.85	2.21
60–69	n=1,463	n=12	n=61	n=1,978	n=12	n=34
smk-	2.75	2.44	2.47	2.05	1.96	1.90
smk+	2.49	2.70	2.56	1.82	1.60	1.76
70+	n=693	n=3	n=36	n=841	n=1	n=21
smk-	2.33	2.19	2.21	1.74	1.21	1.70
smk+	2.28	–	2.23	1.67	–	1.53

n: number of subjects; normals: subjects who reported that they had no diabetes mellitus; DM 1: subjects treated with insulin; DM 2: subjects treated with oral hypoglycaemic agents and/or diet; smk+: smokers; smk-: nonsmokers; FEV_1: forced expiratory volume in one second.

Table 4. – Height-standardized FVC (*l*) according to sex, age, smoking and diabetes mellitus

Age	Men			Women		
yrs	Normals	DM 1	DM 2	Normals	DM 1	DM 2
20–49	n=1,574	n=7	n=21	n=1,710	n=6	n=7
smk-	4.50	4.80	4.17	3.27	2.88	2.91
smk+	4.30	3.53	3.46	3.15	2.98	3.57
50–59	n=1,377	n=15	n=21	n=1,843	n=6	n=15
smk-	3.87	3.32	3.37	2.84	2.24	2.41
smk+	3.64	3.38	3.45	2.69	2.48	2.74
60–69	n=1,463	n=12	n=61	n=1,978	n=12	n=34
smk-	3.44	3.02	3.03	2.55	2.48	2.40
smk+	3.28	3.30	3.20	2.36	1.87	2.20
70+	n=693	n=3	n=36	n=841	n=1	n=21
smk-	3.05	2.79	2.87	2.19	1.32	2.09
smk+	3.02	–	2.90	2.17	–	2.04

n: number of subjects; Normals: subjects who reported that they had no diabetes mellitus; DM 1: subjects treated with insulin; DM 2: subjects treated with oral hypoglycaemic agents and/or diet; smk+: smokers; smk-: nonsmokers; FVC: forced vital capacity.

height-adjusted FEV_1 and FVC compared to the values of the non-diabetic subjects. Because of the small number of diabetic subjects in many of the subgroups, no meaningful significance tests could be employed on these data.

Table 5 presents the results of a multiple regression analysis on FEV_1 and FVC which included age, sex, height, smoking status, body mass index and DM as the independent variables. This regression was employed on a total sample of 11,763 subjects. The effect of both DM 1 and DM 2 on FEV_1 and FVC was highly significant.

Table 6 presents the results of a multiple regression analysis on the subjects without known DM. The regression included the same independent variables as in table 5 except that DM 1 and DM 2 have been replaced by GLU 1 and GLU 2. The association between the raised values of plasma glucose and the

Table 5. – Regression analysis of FVC and FEV_1 of all participants on age, sex, height, body mass index, tobacco consumption, and presence of diabetes mellitus

Independent variable	FVC ml		FEV_1 ml	
	Regression coeff.	p	Regression coeff.	p
Intercept	-2460	–	-1108	–
Age yrs	-34	<0.001	-34	<0.001
Sex 1=male, 0=female	520	<0.001	432	<0.001
Height cm	45	<0.001	33	<0.001
BMI $kg \cdot m^{-2}$	-7	<0.001	1	NS
SMK $g \cdot day^{-1}$	-8	<0.001	-11	<0.001
DM 1 1=DM 1, 0=no DM	-334	<0.001	-239	<0.001
DM 2 1=DM 2, 0=no DM	-184	<0.001	-117	<0.005

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; no DM: subjects who reported that they had no diabetes mellitus; DM 1: subjects treated with insulin; DM 2: subjects treated with oral hypoglycaemic agents and/or diet; BMI: body mass index; SMK: tobacco consumption; NS: not significant.

Table 6. – Regression analysis of FVC and FEV_1 of the subjects without known DM on age, sex, height, body mass index, tobacco consumption, and plasma glucose

Independant variable	FVC ml		FEV_1 ml	
	Regression coeff.	p	Regression coeff.	p
Intercept	-2524	–	-1152	–
Age yrs	-34	<0.001	-34	<0.001
Sex 1=male, 0=female	531	<0.001	439	<0.001
Height cm	45	<0.001	33	<0.001
BMI $kg \cdot m^{-2}$	-7	<0.001	0.5	NS
SMK $g \cdot day^{-1}$	-9	<0.001	-11	<0.001
GLU 1 1=GLU 1, 0=GLU 0	-111	<0.001	-73	<0.001
GLU 2 1=GLU 2, 0=GLU 0	-257	<0.001	-218	<0.001

GLU 0: subjects with plasma glucose lower than 7.8 $mmol \cdot l^{-1}$; GLU 1: subjects with plasma glucose higher than or equal to 7.8 $mmol \cdot l^{-1}$ but lower than 11.1 $mmol \cdot l^{-1}$; GLU 2: subjects with plasma glucose higher than or equal to 11.1 $mmol \cdot l^{-1}$; BMI: body mass index; SMK: tobacco consumption; NS: not significant.

reduction of the lung function was highly significant.

Another multiple regression with all nine independent variables, including DM 1, DM 2, GLU 1, and GLU 2 was performed on the total study sample. In this regression, the impact of DM was weakened compared to the regression in table 5, but it still remained significant for DM 1. The impact of GLU 1 and GLU 2 on FVC and FEV_1 remained highly significant.

There were no significant interactions between DM and the other independent variables.

Discussion

Our results show that in a population study both insulin-dependent and non-insulin-dependent DM (NIDDM) are associated with slightly reduced values of FEV_1 and FVC. The reduction of lung function is slightly more pronounced in diabetic subjects treated with insulin than in diabetic subjects without insulin treatment. This suggests that the severity of DM may influence the degree of lung function impairment. The highly significant association between raised values of plasma glucose and impairment of lung function substantiates this possibility.

Previous spirometric studies on subjects with DM have been conducted on highly selected patients with insulin-dependent DM. Although the majority of the investigators have reported changes in the elastic properties of the lungs and reduced pulmonary diffusing capacity [1, 3, 6, 7], FEV_1 and FVC have mostly been within normal ranges [1–3, 6, 7]. However, in the study of Anasuma *et al.* [5], the subjects with IDDM had slightly but significantly reduced FEV_1 and FVC compared to control subjects. In another study, Schnapf *et al.* [4] were only able to demonstrate a reduction of lung volumes in IDDM patients when the patients also had impaired joint mobility. Consequently, it has been suggested that non-enzymatic glycosylation of connective tissue, especially the collagen, might be responsible for both lung and joint abnormalities [11]. Our findings of an association between raised values of plasma glucose and lung function impairment are in accordance with this hypothesis.

The prevalence of self-reported DM in our study sample was 2.5%, which is slightly higher than the estimated prevalence of DM of 1.0–1.5% in the Danish population. This is due to the age-stratified sampling used in the present study [8] resulting in the bulk of the participants in the age group being between 40–70 yrs, in whom the prevalence of NIDDM can be as high as 4–5% [12]. We are aware of the fact that non-fasting plasma glucose is a very rough estimate of the severity and control of DM. It would have been more useful to employ measurements of glycosylated haemoglobin (HbA_{1c}) as an index of DM control, but such measurements were not performed. Moreover, it would have been desirable to have information on the duration, the clinical history and the type of DM, but unfortunately these aspects were not covered by the questionnaire. However, the age distribution and the treatment regimes strongly suggest that the great majority of the diabetic subjects investigated had NIDDM. This means that some of the subjects in the DM 1 group, especially the ones older than 60 yrs of age were suffering from NIDDM in spite of treatment with insulin.

Due to the small number of diabetic subjects in many of the subgroups (table 3 and 4), the present study does not allow detailed analysis of the impact of DM on ventilatory function in the different age groups. Even so, the slight lung function reduction in the diabetic subjects was present in all age groups (table 3 and 4) and there was no significant interaction between age and DM in the regression analyses.

Many confounding factors might lead to reduction of both FEV_1 and FVC in diabetic subjects. Two of them are obesity and cardiac failure. As many subjects with NIDDM are obese, the reduction of FEV_1 and FVC in NIDDM might therefore be the result of being overweight [13] rather than the result of NIDDM. However, since we have included BMI in the regression model, obesity is unlikely to be an explanation for the observed lung function impairment. In addition, the most pronounced lung function impairment was observed in the DM 1 group, in which BMI was even lower than in the control group. Although none of the diabetic subjects had manifest heart failure during the examination, we cannot exclude that a mild pulmonary congestion was present in some of the diabetic subjects, as ischaemic heart disease is more prevalent in subjects with DM than in normals.

In conclusion, in this population study we have found that FVC and FEV_1 were slightly reduced in subjects without known DM but with raised levels of plasma glucose as well as in subjects reporting to have DM. The lung function reduction was more pronounced in diabetic subjects treated with insulin than in diabetic subjects treated with oral hypoglycaemic agents and/or diet.

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Diabète sucré, glucose plasmatique et fonction pulmonaire dans une étude transversale de population. P. Lange, S. Groth, J. Kastrup, J. Mortensen, M. Appleyard, J. Nyboe, G. Jensen, P. Schnohr.

RÉSUMÉ: Pour apprécier les associations possibles entre le diabète sucré, le glucose plasmatique, la capacité vitale forcée et le VEMS, nous avons analysé les résultats d'une étude transversale de 11.763 sujets. Les sujets avaient 20 ans ou davantage et étaient représentatifs de la population de la ville de Copenhague. Deux cent-quatre-vingt-quatre des participants avaient un diabète sucré dépisté par un questionnaire. Cent-sept sujets, qui ne déclaraient pas avoir un diabète sucré, avaient une concentration plasmatique du glucose supérieure ou égale à 11.1 mmol par litre. On note une légère atteinte de la fonction pulmonaire dans tous les groupes d'âge chez les sujets diabétiques. Cette atteinte est plus marquée chez les sujets diabétiques traités à l'insuline que chez ceux prenant des agents hypoglycémiants oraux, et/ou un régime. Même chez les sujets sans diabète sucré connu, on note une association significative entre la réduction de fonction pulmonaire et l'élévation de la concentration plasmatique en glucose. En moyenne, la capacité vitale forcée et le VEMS sont diminués de 334 ml et de 239 ml chez les sujets diabétiques traités par l'insuline, par comparaison avec 184 ml et 117 ml chez les sujets diabétiques traités les hypoglycémiants oraux et/ou un régime, par comparaison avec des sujets contrôle.

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