Impaired Lung Epithelial Permeability in Diabetics Detected by Technetium-99m-DTPA Aerosol Scintigraphy

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The clearance of inhaled ^{99m}Tc-diethyl triaminepentaacetic acid (DTPA) aerosol from the lungs is used as an index of lung epithelial permeability. We investigated the involvement of the lung in diabetic patients using ^{99m}Tc-DTPA aerosol scintigraphy. **Methods:** A total of 33 diabetic patients were studied. Thirteen had complications such as retinopathy and/or nephropathy (Group A) and 20 were without complications (Group B). As a control group, 20 healthy nonsmokers were studied. Dynamic scintigrams (2 min/frame, up to 30 min) were obtained following inhalation of ^{99m}Tc-DTPA through a radioaerosol delivery system. Time-activity curves were obtained and half-time ($T_{1/2}$) of DTPA was measured from the curves. **Results:** The mean $T_{1/2}$ values (min ± s.d.) were calculated to be 133.05 ± 46.97, 93.67 ± 21.23, 91.97 ± 18.21 (Group A, Group B and controls, respectively). The mean $T_{1/2}$ of Group A was significantly longer than controls ($p < 0.005$) and than that of Group B ($p < 0.005$) indicating decreased epithelial permeability. No such statistical difference was detected between Group B and controls ($p > 0.05$). **Conclusion:** The lung is a target organ in diabetes and lung involvement is closely related to other vascular complications. The presence of lung involvement can be readily detected by ^{99m}Tc-DTPA aerosol scintigraphy.

Key Words: technetium-99m-DTPA; lung epithelial permeability; diabetes mellitus; ^{99m}Tc-DTPA aerosol scintigraphy

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Diabetes mellitus may affect many organs. Retinopathy, nephropathy and neuropathy are well known complications of the underlying microangiopathy. In the literature there have been few and contradictory reports regarding the pulmonary involvement of diabetes (*1*). Technetium-99m-diethyltriaminepentaaceticacid (^{99m}Tc-DTPA) aerosol scintigraphy is a noninvasive, accurate method that evaluates the permeability of lung epithelial membranes (*2*). This manuscript reports the relationship between lung epithelial permeability and vascular complications in 33 diabetic patients.

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MATERIALS AND METHODS

A total of 33 diabetic patients (25 female, 8 male, 19–72 yr) participated in this study after giving informed consent. None of the patients had clinical evidence of past or present respiratory disease. Thirteen patients had vascular complications (Group A; n = 7 with nephropathy + retinopathy + neuropathy, n = 3 nephropathy + retinopathy, n = 2 neuropathy, n = 1 retinopathy) while 20 patients were free of vascular complications (Group B). The presence of retinopathy was confirmed by fundoscopy and flourescein angiography. The diagnosis of neuropathy and nephropathy was based on the findings from physical and laboratory examinations. Thirty patients were life-long nonsmokers. In three smokers, smoking was discontinued 6 wk prior to the study. Twenty healthy nonsmokers (9F, 11M, age range 22–31 yr) were studied as control subjects.

Technetium-99m-DTPA (CIS, France) was chelated by introducing 30 mCi (1110 MBq) of sodium $^{99m}TcO_4^-$ into 2–3 ml of normal saline. The quality control of ^{99m}Tc-DTPA was performed using thin-layer chromatography. Technetium-99m-DTPA was placed in the nebulizer reservoir of a commercially available system (Venticis II, CIS, France). Aerosols with a mass median diameter of 0.8 μ were produced with an oxygen inflow of 9 liter/min. Subjects inhaled the radioaerosol for 4–5 min and then were disconnected from the system. The procedure resulted in the deposition of 0.87–2.7 mCi of ^{99m}Tc-DTPA in the lungs. The subjects were placed supine over a gamma camera (Toshiba GCA 601E) with a low-energy, all-purpose collimator and lung fields were imaged in posterior projection. Clearance from the lungs was measured for 30 min (2 min/frame) following termination of inhalation. Areas of interest of equal size were placed over the right and left lung. Radioactivity was first corrected for ^{99m}Tc decay and plotted as a logarithmic function of time. An exponential line of best fit was determined by regression analysis and pulmonary half-life ($T_{1/2}$) was calculated from the slope of the line using the formula $N = Noe^{-kt}$ (where No is initial activity in the lung, N is the activity at time t and k is the slope) as an indicator of lung epithelial permeability for each lung after which an average of left and right lung was calculated. In determining differences between the diabetic subjects and controls as well as between diabetic subjects with and without complication, the Student's t-test for unpaired data was used.

TABLE 1
Details of Diabetic Patients with Complication (Group A)

Patient no.	Age/Sex	Clearance rate $T_{1/2}$ (min)	Duration of diabetes (yr)	Complication
1	56/F	108.79	10	Neuropathy
2	72/M	87.72	18	Neuropathy
3	66/M	104.21	2	Retino + Nephro + Neuro
4	62/F	80.76	12	Retino + Nephro + Neuro
5	60/F	111.59	11	Retino + Nephro + Neuro
6	61/F	96.78	11	Retino + Nephro + Neuro
7	27/M	108.45	12	Retinopathy
8	23/F	244.87	8	Retino + Nephro + Neuro
9	48/F	182.37	9	Retino + Nephro + Neuro
10	29/F	169.85	8	Retino + Nephro
11	28/M	138.87	10	Retino + Nephro
12	28/M	123.97	16	Retino + Nephro + Neuro
13	19/F	171.53	7	Retino + Nephro

Neuro = neuropathy, Nephro = nephropathy and Retino = retinopathy.

RESULTS

The binding of $^{99m}TcO_4^-$ to DTPA was more than 96% as judged by thin-layer chromatography. In all diabetic patients as well as normals, clearance curves were found to be monoexponential, as judged by the best fit method. Clinical characteristics of diabetic patients and $T_{1/2}$ values are seen in Tables 1 and 2. Comparative clearance data of control subjects with diabetic Groups A and B are illustrated in Figure 1. In normal subjects the mean $T_{1/2}$ value was found to be 91.97 ± 18.21 min (± s.d.). Corresponding values were 133.05 ± 46.97 min and 93.67 ± 21.23 min for Group A and Group B.

TABLE 2
Details of Diabetic Patients Without Complication (Group B)

Patient no.	Age/Sex	Clearance rate $T_{1/2}$ (min)	Duration of diabetes (yr)
1	58/F	65.50	8
2	64/F	155.03	6
3	52/F	97.06	5
4	41/F	92.15	5
5	64/F	80.95	18
6	64/F	105.16	22
7	58/F	93.39	6
8	62/F	67.28	8
9	48/F	67.28	16
10	58/M	70.57	2
11	55/F	105.80	9
12	58/M	69.85	8
13	58/F	80.77	3
14	66/F	101.76	12
15	60/F	110.88	15
16	30/F	106.61	12
17	34/F	106.61	8
18	22/F	106.12	13
19	36/M	99.56	3
20	32/F	91.18	5

The Relationship of Pulmonary Epithelial Permeability to Existing Diabetic Complications

The mean $T_{1/2}$ value of Group A was significantly longer than that of normals ($p < 0.005$) and Group B ($p < 0.005$). On the other hand, no such significance was found between controls and Group B ($p > 0.05$). In other words, pulmonary epithelial permeability was significantly reduced in the complicated group.

The Influence of Duration of Diabetes on Pulmonary Epithelial Permeability

Poor correlation was found between the duration of diabetes and $T_{1/2}$ values in diabetic patients ($r = 0.06$).

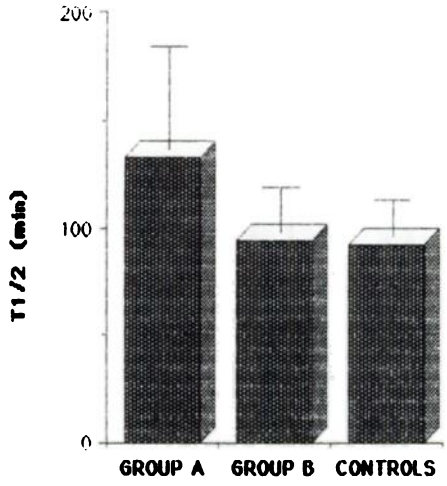

FIGURE 1. Comparative clearance rate ($T_{1/2}$, min ± s.d.) of normal subjects with the diabetic group.

DISCUSSION

Changes in the permeability of the pulmonary epithelial membrane are detected following inhalation of submicronic ^{99m}Tc-DTPA aerosol. When ^{99m}Tc-DTPA reaches the pulmonary epithelium, it diffuses from the airspace to the vascular space, equilibriates with the extracellular fluid and is filtered by the kidneys. The rate at which ^{99m}Tc-DTPA clears from the lungs decreases or increases when pulmonary epithelial permeability is decreased or increased, which makes it a useful tool in detecting early stages of diseases involving the lung membrane (*2*). Smoking, interstitial lung diseases, sarcoidosis, long-term use of free-base cocaine and high-dose bleomycine may significantly alter lung epithelial permeability to ^{99m}Tc-DTPA (*3–7*). Lung epithelial permeability can also be assessed by carbon monoxide (CO) diffusing capacity which can provide information about the ability of gas to diffuse across the alveolar-capillary membrane. On the other hand, the scintigraphic method is much simpler than that of CO diffusing capacity. Moreover, because of the effect of hemoglobin levels on CO diffusing capacity, the measured value should be corrected for hemoglobin (*2,8*).

Reports regarding pulmonary changes in patients with diabetes mellitus are rather limited. It has been reported that the transfer factor for carbon monoxide in diabetic patients with microangiopathy is significantly lower than in a matched group without this complication (*8*). In other studies, decreased elasticity of the lungs due in part to collagen glycosylation was reported (*1,9–10*). In rats with experimentally induced diabetes mellitus, considerable ultrastructural changes were observed, primarily of the type II pneumocytes (*11*). Vracko et al. (*12*) reported that diabetes leads to thickening of the alveolar epithelial and capillary basal lamina. Thickening of the alveoli was also demonstrated in streptozotosin-induced diabetes mellitus in rats (*13*). The mechanism of development of diabetic degenerative complications is still not completely understood. Capillary basement membrane thickening, nonenzymatic glycosylation of tissue proteins, abnormalities of endothelial cells and platelets and increased damage by free radicals might be the underlying basis for the reduced permeability. Similar changes were seen in susceptible target organs such as the kidney and retina.

We conclude that measurement of ^{99m}Tc-DTPA lung clearance can be a useful technique to assess injury in diabetic patients and that impaired lung epithelial permeability seems to be related to the existing diabetic complications but not to the duration of diabetes. Monoexponential clearance curves found in such patients suggested that the diabetic involvement of the lung is in a diffuse pattern, rather than a patchy pattern.

The clinical implications of decreased lung epithelial permeability in diabetic patients in terms of respiratory disease are presently unknown. Since normal lung mechanism and gas exchange are influenced by the integrity of the pulmonary connective tissue and microvasculature, it is expected that the patients with impaired epithelial permeability would have some pulmonary problems. However, all our patients denied respiratory symptoms. It is assumed that changes in pulmonary epithelial permeability precede clinical symptoms and such patients might be asymptomatic at rest, but might have reduced exercise tolerance. Further studies measuring exercise-induced changes in such patients and the effect of anti-diabetic medication and glysemic control on lung epithelial permeability is under investigation at our institution.

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