Original Research Paper

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Nuclear Medicine

EVALUATION OF EPITHELIAL PERMEABILITY OF LUNGS IN DIABETIC PATIENTS WITHOUT PULMONARY SYMPTOMS USING TECHNETIUM-99M DIETHYLENE TRI AMINE PENTA ACETIC ACID (DTPA) AEROSOL SCINTIGRAPHY.

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ABSTRACT

Introduction: Diabetes is the most common of all endocrine diseases and is one of the leading causes of death in developed countries.[1] Diabetes related complications are broadly categorized into microvascular and macrovascular. The pathophysiology behind all of these complications is vascular damage.[2,3] **Aerosol Lung Scintigraphy:** was done in many Nuclear Medicine departments for diagnosis of acute pulmonary embolism as a part of ventilation perfusion (V/Q) scan. Diabetic patients had a reduced pulmonary diffusing capacity for carbon monoxide (DLCO), as vascular injury of pulmonary capillaries causes decreased vascular permeability.[4,5] Changes in the permeability of the pulmonary epithelial membrane can be detected following the inhalation of submicronic Tc-99m DTPA. After inhalation, Tc-99m DTPA aerosol reach pulmonary epithelium, diffuse from the airspace to the vascular space and excretes through kidneys. The clearance rate of the Tc-99m DTPA aerosols depends on the pulmonary epithelial permeability in such a way that the clearance increases when there is increased permeability and decreases when there is decreased permeability. Hence, Tc-99m DTPA aerosol scintigraphy is a useful tool in the evaluation of disease involvement of pulmonary epithelial membrane. In this study, we intended to look for the changes in permeability of pulmonary epithelial membrane in the patients diagnosed to have diabetes mellitus and who do not have any respiratory or cardiac related symptoms when compared to the normal healthy population by using Tc-99m DTPA aerosol scintigraphy. **Aim/ Purpose:** To evaluate the lung epithelial permeability in patients with diabetes without pulmonary symptoms by using Technitium-99m Diethylene Triamine Pentaacetic Acid (DTPA) aerosol scintigraphy. **Material And Methods:** This was a cross-sectional comparative study conducted at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India. in patients diagnosed with diabetes mellitus satisfying inclusion (18-60 years and without any disease) and exclusion criteria (smoking, pregnancy, breastfeeding and pulmonary or cardiac disease, respiratory infections within 6 weeks) who are in follow-up in diabetic clinic from February 2018 to October 2019, along with healthy volunteers, were enrolled to participate in the study. Tc-99m DTPA dynamic aerosol lung scintigraphy was performed in all of them using a dual-headed gamma camera. **Image Interpretation:** Images were analyzed by a qualified nuclear medicine physician, A time-activity curve (TAC) was created using the background-corrected ROI. The curve was smoothed and a mono-exponential fitting was created. With the time- activity curve, Tc-99m DTPA clearance $T_{1/2}$ was calculated in both lungs separately and the mean value of both lungs was considered as clearance $T_{1/2}$ of the study. Decay correction was applied while calculating $T_{1/2}$. **Statistical Analysis:** An unpaired T-test was used to compare the means of the two groups. If p-value was less than 0.05, the statistical difference was considered significant. The analysis was done using SPSS software edition 19. RESULTS: The clearance $T_{1/2}$ values of all participants, which were obtained from the dynamic Tc-99m DTPA aerosol lung scintigraphy, were initially analysed using a chi- square test to check the normality of data. The chi-square test showed that the data was normally distributed. As it was numeric and parametric data, the mean $T_{1/2}$ between diabetic patients and healthy volunteers was compared using unpaired T-test. The mean (S.D) clearance $T_{1/2}$ in diabetic patients was 55.71 (15.42) minutes and in healthy volunteers was 47.64 (12.72) minutes. The difference in mean values was statistically significant ($p = 0.01$). **Conclusion:** Our study shows significantly reduced lung epithelial permeability in diabetic patients, especially in those who have diabetes for a longer duration and in those with presence of diabetes related complications.

KEYWORDS : Tc-99m DTPA aerosol lung scintigraphy, lung epithelial permeability, diabetes

INTRODUCTION:

Diabetes is the most common of all endocrine diseases and is one of the leading causes of death in developed countries.[1] Diabetes mellitus is characterized by an increase in blood glucose levels, due to the defects in insulin secretion, insulin action, or both. Insulin is the hormone that decreases the blood sugar levels and secreted from pancreatic beta cells. There are two types of diabetes, type I and type II. Type 1 diabetes is caused by the destruction of pancreatic beta cells by the immune cells. Type 2 diabetes is caused by the peripheral resistance to insulin, and insulin resistance in type 2 diabetes patients increases the demand for insulin. Gestational diabetes is another variant that is seen in pregnant females. Type 2 diabetes is more common compared to type 1 diabetes.

According to the data from the International Diabetic Federation, there were over 72,946,400 cases of diabetes in India in 2017.[6] The mortality and morbidity in diabetic patients is mostly because of the diabetes related complications.[7]

Diabetes related complications are broadly categorized into microvascular and macrovascular. Microvascular complications occur more frequently when compared to macrovascular complications.[8] Microvascular complications comprises of retinopathy, neuropathy and nephropathy whereas macrovascular complications include cardiovascular disease, cerebrovascular disease and peripheral artery disease. Diabetic foot syndrome is another complication that is defined as the presence of foot ulcer associated with neuropathy, peripheral artery disease, and infection.[9] Other complications in diabetes mellitus that are not related to vascular complications include resistance to infections and birth complications in women with gestational diabetes.[7]

Maximum mortality and morbidity in diabetic patients are due to neuropathy, retinopathy, nephropathy, and cardiovascular dysfunction. The pathophysiology behind all of these complications is vascular damage.[2,3] Even though there is a large capillary network in the lung, patients do not usually present with pulmonary complications. This is mainly because of the great micro vascular reserve of alveolar- capillary system.[10] When there are other comorbidities like hypoxia, pneumonia, asthma, chronic obstructive pulmonary disease and fluid overload because of right heart failure, loss of this microvascular reserve may become clinically important.[11]

Aerosol lung scintigraphy was done in many Nuclear Medicine departments for diagnosis of acute pulmonary embolism as a part of ventilation perfusion (V/Q) scan. Diabetic patients had a reduced pulmonary diffusing capacity for carbon monoxide (DLCO), as vascular injury of pulmonary capillaries causes decreased vascular permeability.[4,5] Changes in the permeability of the pulmonary epithelial membrane can be detected following the inhalation of submicronic Tc-99m DTPA. After inhalation, Tc-99m DTPA aerosol reach pulmonary epithelium, diffuse from the airspace to the vascular space and excretes through kidneys. The clearance rate of the Tc-99m DTPA aerosols depends on the pulmonary epithelial permeability in such a way that the clearance increases when there is increased permeability and decreases when there is decreased permeability. Hence, Tc-99m DTPA aerosol scintigraphy is a useful tool in the evaluation of disease involvement of pulmonary epithelial membrane.
In this study, we intended to look for the changes in permeability of pulmonary epithelial membrane in the patients diagnosed to have diabetes mellitus and who do not have any respiratory or cardiac related symptoms when compared to the normal healthy population by using Tc-99m DTPA aerosol scintigraphy.

AIM OF THE STUDY:
To evaluate the lung epithelial permeability in patients with diabetes without pulmonary symptoms by using Technitium-99m Diethylene Triamine Pentaacetic Acid (DTPA) aerosol scintigraphy.

Objective Of The Study:
To compare the mean elimination half-life ($T_{1/2}$) of Technitium-99m Diethylene Triamine Pentaacetic Acid (DTPA) aerosols in diabetic patients without pulmonary symptoms and apparently normal subjects.

MATERIALS AND METHODS :
Study Design And Study Participants:
This is a Single-Centre Cross-Sectional Comparative Study conducted at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.. Consecutive patients diagnosed with diabetes mellitus satisfying inclusion and exclusion criteria who are in follow-up in diabetic clinic from February 2018 to October 2019, along with healthy volunteers, were enrolled to participate in the study. All of the patients were being treated in the diabetic clinic maintained under the departments of General Medicine and Endocrinology. Tc-99m DTPA dynamic aerosol lung scintigraphy was performed in all of them using a dual-headed gamma camera. The study was approved by the Institute Ethics Committee- (JIP/IEC/2017/408).
A. Study design: Cross-sectional comparative study.

B. Study participants:
1) Number of groups studied: Two

2) Inclusion criteria:
Group 1 (Diabetic group):
I. Diagnosed cases of diabetes for at least 5 years and without any pulmonary and cardiac symptoms at the time of the study.
II. Age more than 18 years and up to 60 years.

Group 2 (Healthy volunteer group):
I. Apparently normal subjects with age more than 18 years and up to 60 years.

3) Exclusion Criteria:
I. History of smoking.
II. Pregnancy and breastfeeding.
III. Known pulmonary or cardiac disorders.
IV. Respiratory tract infections within 6 weeks.

4) Sampling:
a. Sampling population: Cases of diabetes without pulmonary symptoms presenting to the diabetic clinic between February 2018 to October 2019 and healthy volunteers.
b. Sample size calculation: After observing data from the previous studies, considering the mean values in group 1 as 109.91 minutes (SD - 38.43) and group 2 as 91.97 minutes (SD - 18.21), assuming 95% confidence interval with an alpha error of 5, power of the test as 80 %, ratio between group 2 and group 1 as 0.5, the sample size was calculated to be 87 (58 in group 1 and 29 in group 2). The calculation of sample size was done using Open Epi Software version 3.1.
c. Sampling technique: Consecutive patients attending diabetic clinic and satisfying the inclusion and exclusion criteria.

Study Procedure:
Patients diagnosed with diabetes mellitus for at least 5 years and who were under follow up in the diabetic clinic were evaluated clinically and explained about the study. Those who were interested in participating were referred to the Department of Nuclear Medicine for dynamic aerosol lung scintigraphy. Healthy volunteers who were interested to participate were also referred to the Department of Nuclear Medicine. Some of them were working staff in different departments and others were attendants of diabetic patients. After noting down the details and clinical history of the patients, consent was taken for the study procedure. Diabetes related complications were determined by using clinical and laboratory data. In diabetic patients, non-contrast computed tomography (NCCT) of the thorax was performed after clinical evaluation. The CT system that we used was the part of the SPECT/CT machine, and it was equipped with a six-slice multi-detector CT. The acquisition parameters that we used for CT acquisition were 130 kV, 100 mA, the pitch of 1, 512 × 512 matrix and standard filters. The CT images were reconstructed with reconstruction kernel B60s and 1 mm slice thickness in all three planes. The NCCT images of the thorax were evaluated to look for any major structural changes. After evaluating the CT, if there were no significant changes, the patients were subjected to dynamic aerosol lung scintigraphy. Aerosol lung scintigraphy was performed by using Tc-99m DTPA aerosols.We prepared the radiopharmaceutical (Tc-99m DTPA) and checked it for chemical impurities by performing quality control using the paper chromatography technique.

The radiopharmaceutical, with more than 90% radiochemical purity, was used for aerosol preparation. The aerosol was prepared from Tc-99m DTPA solution using the Omron compressor NE-C900 pro nebuliser which can produce aerosol with a median diameter of 2 micrometers. The flow rate was 10-12 litre per minute. The patient was advised to sit on the stool and nebuliser was connected to patient's mouth and nose with a nebuliser mask set. Before connecting the nebuliser, the patient was covered with a plastic apron to avoid the contamination if it happens. 25 - 30 mCi of Tc-99m DTPA in 3 ml of 0.9 % saline solution was placed in the nebuliser which generates the aerosols, and the patient was instructed to inhale the aerosols by deep tidal breathing for 3 to 4 minutes in sitting position. Before adding the Tc-99m DTPA solution in nebuliser, patients were acclimatised to the procedure by using normal saline instead of Tc-99m DTPA. After inhalation of radio-aerosol for 3 to 4 minutes under supervision, nebuliser machine was stopped, and the equipment and apron were removed from the patient while maintaining proper radiation safety precautions. The patient was advised to wash the mouth with water without contaminating him/ herself.

After aerosol inhalation, the patient was shifted to the acquisition room and dynamic images of the thorax were acquired in anterior and posterior views for 30 minutes using dual-headed gamma camera (Seimens, Symbia T6). The gamma camera was equipped with low energy high-resolution parallel hole collimator. A 15% energy window was set around 140 KeV. Dynamic images of the thorax region were acquired at 1 minute per frame for 30 minutes. A matrix size of 256x256 was chosen. This was followed by a spot view static image of thorax and abdomen after 90 minutes. The images were processed in Siemens workstation.In healthy volunteers, Tc-99m DTPA aerosol lung scintigraphy was performed in a similar manner as that of diabetic patients. However, NCCT of the thorax was not performed in them.

IMAGE INTERPRETATION:

Images were analysed by a qualified nuclear medicine physician with experience in nuclear medicine reporting for 18 years. Dynamic images were analysed in cine mode, followed by the planar images. The geometric progression mean (GM) image was reconstructed using software provided in the Siemens workstation. A region of interest (ROI) was drawn over the lung excluding the central medial aspect of the lung (for large airways). The brightness of the image was adjusted in such a way that there was an optimal visualisation of the lung periphery for marking the region of interest. Background-corrected images were considered for final interpretation after subtracting background activity from ROI drawn over the shoulder area. A time-activity curve (TAC) was created using the background-corrected ROI. The curve was smoothed and a mono-exponential fitting was created. With the time- activity curve, Tc-99m DTPA clearance $T_{1/2}$ was calculated. A similar procedure was repeated for the other lung and the mean value of both lungs was considered as clearance $T_{1/2}$ of the study. Decay correction was applied while calculating $T_{1/2}$.

Statistical Analysis:

Continuous data was expressed as mean ± S.D. Categorical variables were expressed as proportions. An unpaired T-test was used to compare the means of the two groups. If p-value was less than 0.05, the statistical difference was considered significant. The analysis was done using SPSS software edition 19.

RESULTS:

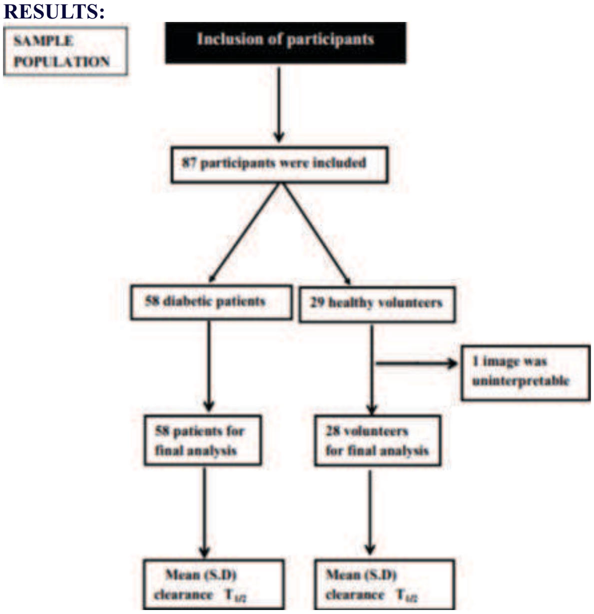

Table 1: Baseline Characteristics Of All Participants

CHARACTERISTIC	VALUE
Total number of participants	86
Sex	
Male: no. (%)	18 (21 %)
Female: no. (%)	68 (79%)
Age- years	
Mean (SD):	49.07 (8.00)
Mean age of male participants:	50.17 (8.09)
Mean age of female participants:	48.78 (8.01)

Table 2: Baseline Characteristics Of Healthy Volunteers

CHARACTERISTIC	VALUE
No of Healthy volunteers	28
Sex	
Male: no. (%)	03 (10%)
Female: no. (%)	25 (90%)
Age- years	
Mean (SD):	47.10 (7.57)
Mean age of male volunteers:	54.00 (6.55)
Mean age of female volunteers:	46.28 (7.36)

Table 3: Baseline Characteristics Of Diabetic Patients.

CHARACTERISTIC	VALUE
No of diabetic patients	58
Sex	
Male: no. (%)	15 (26%)
Female: no. (%)	43 (74%)
Age- years	
Mean (SD):	50.02 (8.09)
Mean age of male patients:	49.40 (8.33)
Mean age of female patients:	50.23 (8.13)
Duration of diabetes mellitus - years	
Mean (SD)	10.62 (4.18)
No of patients with duration of diabetes more than 10 years:	24
No of patients with duration of diabetes less than 10 years:	34
Type of medication intake	
On combined oral hypoglycaemic agents:	35
On insulin therapy:	23
Diabetic related complications	
No of patients without complications:	32
No of patients with complications:	26
Neuropathy:	25
Retinopathy:	5
Nephropathy:	3
Neuropathy and retinopathy:	4
Neuropathy and nephropathy:	2
Neuropathy, retinopathy and nephropathy:	1
Comorbidities: No of patients	
Hypertension	27
Hypo/hyperthyroidism	2

A total of 87 participants were initially considered for inclusion in the study. One of the healthy volunteer images could not been analyzed due to accumulation of tracer activity in the stomach. So, data of the 86 participants was included for the final analysis. All diabetic patients were referred from a diabetic clinic.

Out of 86 participants, there were 18 (20%) male and 68 (80%) female participants. Out of 86 participants, 58 were diabetic patients and 28 were healthy volunteers. Among 58 diabetic patients, 43 (74%) were females and 15 (26%) were male patients. Among 28 healthy volunteers, 25 (90%) were females and 3 (10%) were males.

The mean (S.D) age of all participants was 49.07 (8.00) years. The mean age of male participants was 50.17 (8.09) years. The mean age of female participants was 48.78 (8.01) years. The mean age of diabetic patients was 50.02 (8.09) years. The mean age of males in the diabetic patients was 49.40 (8.33), and the mean age of females in the diabetic patients was 50.23 (8.13) years. The mean age of healthy volunteers was 47.1 (7.57) years, and among them mean ages of males and females were 54.0 (6.55) and 46.28 (7.36) years, respectively.

Among the 58 diabetic patients, 26 (45%) patients had diabetic-related complications and 32 (55%) patients did not have any diabetic-related complications. Among 26 patients who had complications, 25 (96%) had neuropathy, 5 (19%) had retinopathy and 3 (12%) had nephropathy. 4 patients had retinopathy and neuropathy, 2 patients had nephropathy and neuropathy, and 1 patient had neuropathy, retinopathy and nephropathy.

Among the 26 patients who had diabetic-related complications, 4 (15%) were male patients and 22 (85%) were female patients. Among the 32 patients who did not have diabetic-related complications, 11 (34%) were male patients and 21 (66%) were female patients. The mean (S.D) age of the patients who had diabetic-related complications is 51.31 (8.25) years and among them who did not have any diabetic-related complications was 48.97 (7.94) years.

Among 58 diabetes patients, 34 (58%) patients were suffering from diabetes for less than or equal to 10 years, and 24 (42%) patients were suffering from diabetes for more than 10 years. Among the 34 diabetic patients who had diabetes for less than or equal to 10 years of duration, 9 (26%) were males and 25 (74%) were females. Among 24 diabetic patients who were suffering from diabetes for more than 10 years of duration, 6 (25%) were males and 18 (75%) were females. The mean (S.D) age in those who had a duration of diabetes for less than or equal to 10 years was 48.35 (7.59) years and those who had a duration of diabetes for more than 10 years was 52.38 (7.35) years.

The mean (S.D) duration of diabetes among 58 diabetic patients was 10.62 (4.18) years. Among the 58 diabetic patients, 35 (61%) were using oral hypoglycaemic agents, and 23 (39%) were using insulin for their hyperglycaemic control. Among the 35 diabetic patients who were on oral hypoglycaemic agents, 9 (25%) were males and 26 (75%) were females. Among 23 diabetic patients who were using insulin, 6 (27%) were males and 17 (73%) were females. The mean (S.D) age of diabetic patients who were on insulin was 52.09 (7.43) years, and who were on oral hypoglycaemic agents was 48.66 (7.68) years.

Among 58 diabetic patients, 27 had hypertension, 2 had hypothyroidism. Among 2 hypothyroid patients, 1 had a history of hyperthyroidism for which treated with radioiodine. Hypertensive patients were on anti-hypertensive medication, and hypothyroid patients were on Levothyroxine supplementation.

The clearance $T_{1/2}$ values of all participants, which were obtained from the dynamic Tc-99m DTPA aerosol lung scintigraphy, were initially analysed using a chi- square test to check the normality of data. The chi-square test showed that the data was normally distributed. As it was numeric and parametric data, the mean $T_{1/2}$ between diabetic patients and healthy volunteers was compared using unpaired T-test. The mean (S.D) clearance $T_{1/2}$ in diabetic patients was 55.71 (15.42) minutes and in healthy volunteers was 47.64 (12.72) minutes. The difference in mean values was statistically significant ($p = 0.01$).

The mean (S.D) clearance $T_{1/2}$ in the diabetic patients who had diabetic-related complications like neuropathy, retinopathy, and nephropathy was 61.04 (15.28) minutes, and in diabetic patients who did not have any diabetic-related complications was 51.38 (14.35) minutes. The difference in the mean was statistically significant ($p = 0.01$). The difference in mean clearance $T_{1/2}$ between diabetic patients with dictates related complications and healthy volunteers was also significant ($p = 0.01$). The difference in mean clearance $T_{1/2}$ between healthy volunteers and diabetic patients who did not have diabetic-related complications was not significant ($p > 0.05$).

The mean (S.D) clearance $T_{1/2}$ in those who had diabetes for more than 10 years was 61.33 (14.78) minutes and in those who had diabetes for less than or equal to 10 years was 51.74 (14.81) minutes. The mean difference was statistically significant ($p = 0.01$). The difference in mean clearance $T_{1/2}$ was also significant among the healthy volunteers and diabetic patients with the duration of diabetes for more than 10 years ($p = 0.003$). But no significant difference was found between healthy volunteers and diabetic patients with duration of diabetes less than or equal to 10 years ($p > 0.05$).

The mean (S.D) clearance $T_{1/2}$ in diabetic patients who were using insulin was 52.64 (15.44) minutes and those who are using oral hypoglycaemic agents was 59.76 (14.72) minutes. The mean difference was not statistically significant ($p = 0.08$).

We calculated the $T_{1/2}$ separately for both lungs initially, and then the average was taken as a $T_{1/2}$ value for the participant. In 80 participants, the difference between the $T_{1/2}$ values of both lungs was not more than 6 minutes. But in 6 participants, the difference between both lungs is more than 6 minutes. Out of 6, 5 were diabetic patients and 1 was a healthy volunteer. The maximum difference of 14 minutes was observed in a diabetic patient who did not have any known diabetes related complications.

Table 4: Comparison Of Characteristics Between Diabetic Patients And Healthy Volunteers.

	Diabetic patients	Healthy volunteers
Number of participants	58	28
Male : Female	15:43	3:25
Mean age (S.D) in years	50.02 (8.09)	47.10 (7.57)
Mean $T_{1/2}$ (S.D) in minutes	55.71 (15.42)	47.64 (12.72)

Table 5: Comparison Of Characteristics Between Diabetic Patients With Diabetes Related Complications And Diabetic Patients Without Complications.

	Diabetic patients with diabetes related complications	Diabetic patients without complications
Number of participants	26	32
Male : Female	4:22	11:21
Mean age (S.D) in years	51.31 (8.25)	48.97 (7.94)
Mean $T_{1/2}$ (S.D) in minutes	61.04 (15.28)	51.38 (14.35)

Table 6: Comparison Of Characteristics Between Healthy Volunteers, Diabetic Patients With Diabetes Related Complications And Diabetic Patients Without Complications.

	Healthy volunteers	Diabetics (without complications)	Diabetics (with complications)
Number of participants	28	32	26
Male : Female	3:25	11:21	4:22
Mean age (S.D) in years	47.10 (7.57)	48.97 (7.94)	51.31 (8.25)
Mean $T_{1/2}$ (S.D) in minutes	47.64 (12.72)	51.38 (14.35)	61.04 (15.28)

Table 7: Comparison of characteristics between diabetic patients with duration of diabetes for less than or equal to 10 years and diabetic patients with duration of diabetes for more than 10 years.

	Duration of diabetes for more than10 years	Duration of diabetes for less than or equal to 10 years
Number of participants	24	34
Male : Female	6:18	9:25
Mean age (S.D) in years	52.38 (7.35)	48.35 (7.59)
Mean $T_{1/2}$ (S.D) in minutes	61.33 (14.78)	51.74 (14.81)

Table 8: Comparison Of Characteristics Between Diabetic Patients On Insulin And Diabetic Patients On Only Oral Hypoglycaemic Agents.

	On insulin	Only on oral hypoglycaemic agents
Number of participants	23	35
Male : Female	6:17	9:26
Mean age (S.D) in years	52.09 (7.43)	48.66 (7.68)
Mean $T_{1/2}$ (S.D) in minutes	59.76 (14.72)	52.64 (15.44)

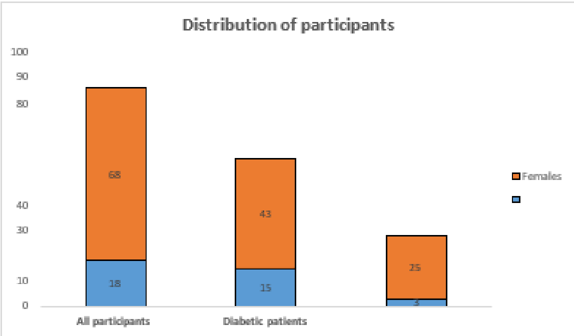

Figure 1: Bar diagram showing total number of participants and participants in each group along with gender distribution.

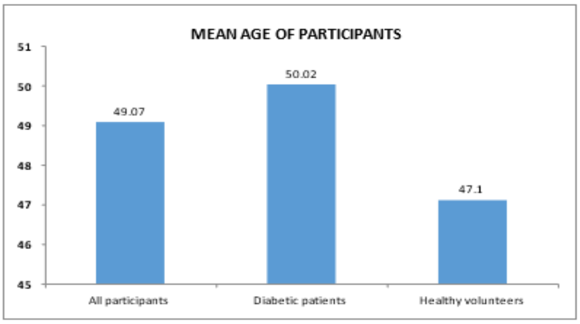

Figure 2: Bar diagram showing mean age of males and females in all the participants and individual groups.

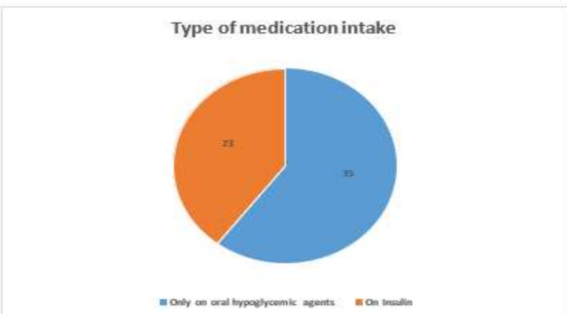

Figure 3: Pie diagram showing the proportion of diabetic patients on insulin therapy and only on oral hypoglycaemic agents.

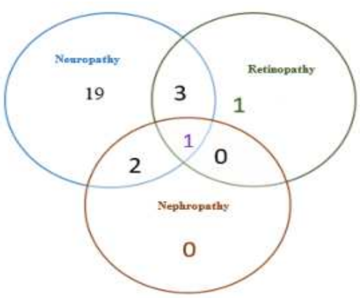

Figure 4: Venn diagram showing distribution of complications among diabetic patients.

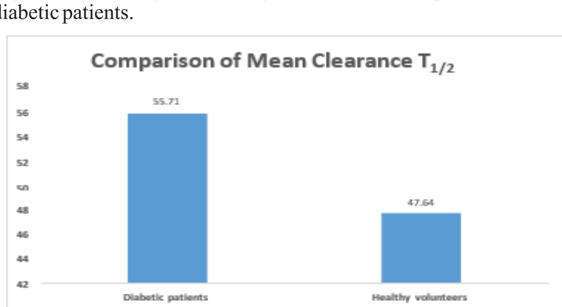

Figure 5: Bar diagram showing difference in mean clearance $T_{1/2}$ (minutes) in diabetic patients and healthy volunteers.

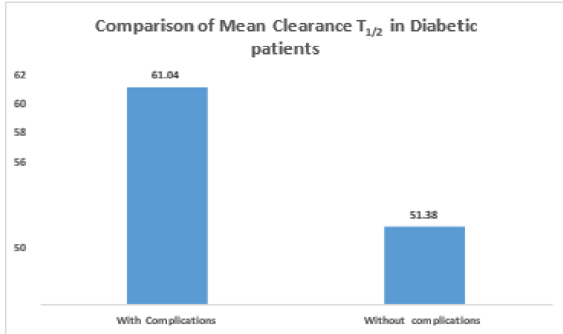

Figure 6: Bar diagram showing difference in mean clearance $T_{1/2}$ (minutes) in diabetic patients with complications like neuropathy, retinopathy and nephropathy, and without any complications.

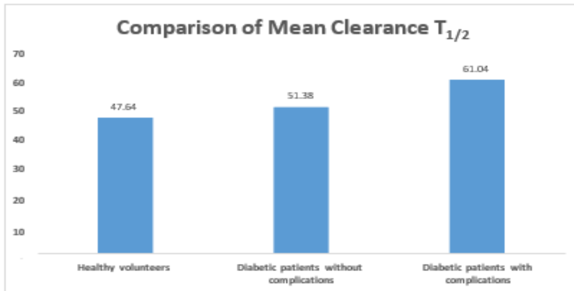

Figure 7: Bar diagram showing difference in mean clearance $T_{1/2}$ (minutes) among healthy volunteers, and diabetic patients with and without complications.

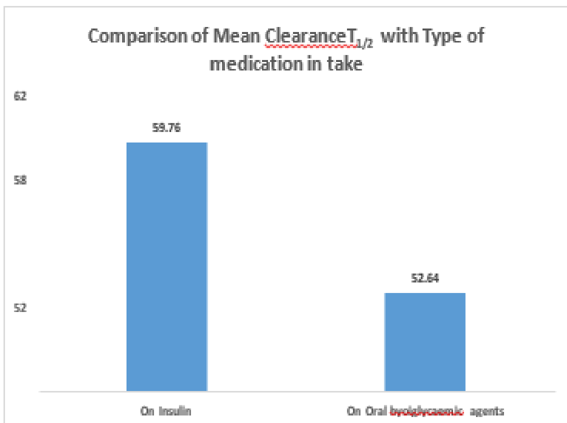

Figure 8: Bar diagram showing difference in mean clearance $T_{1/2}$ (minutes) among diabetic patients consuming insulin and oral hypoglycaemic agents.

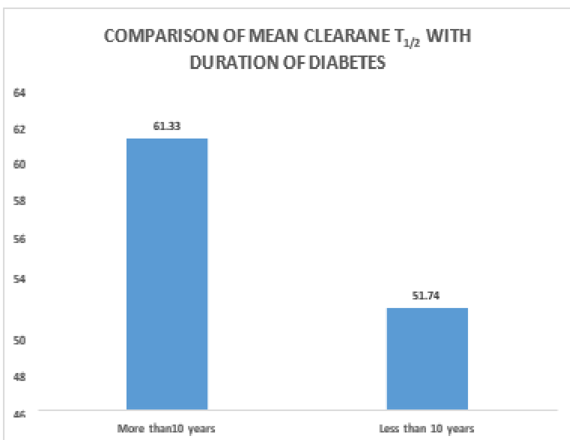

Figure 9: Bar diagram showing difference in mean clearance $T_{1/2}$ (minutes) in diabetic patients with duration of diabetes more than 10 years and less than 10 years.

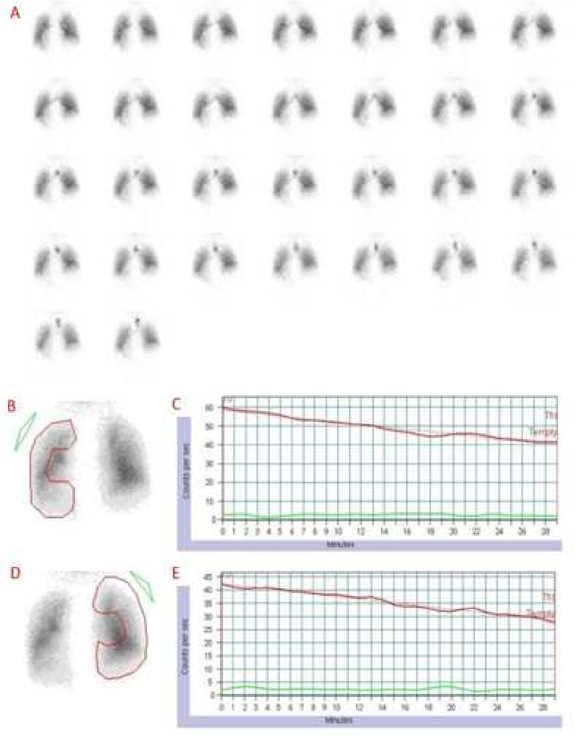

Figure 10: 48 year old healthy female volunteer. Tc-99m DTPA aerosol lung scintigraphy, dynamic images acquired for 1 minute per frame (A) showed aerosols in bilateral lungs and primary bronchi. ROI (B) of the left lung and TAC (C) of the left lung showing the clearance pattern. ROI (D) of the right lung and TAC (E) of the right lung showing the clearance pattern. $T_{1/2}$ of the left lung is 46 minutes and right lung is 44 minutes.

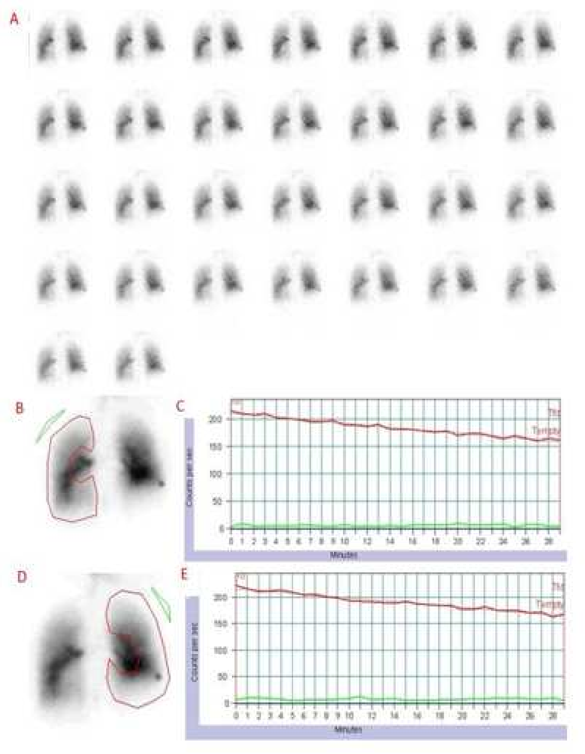

Figure 11: 52 year old female diagnosed with diabetes mellitus for 8 years without any diabetes related complications, and currently on oral anti- hypoglycaemic agents. Tc-99m DTPA aerosol lung scintigraphy, dynamic images (A) showed aerosols in bilateral lungs. ROI

(B) of the left lung and TAC (C) of the left lung showing the clearance pattern. ROI (D) of the right lung and TAC (E) of right lung showing the clearance pattern. $T_{1/2}$ of the left lung is 57 minutes and the right lung is 59 minutes.

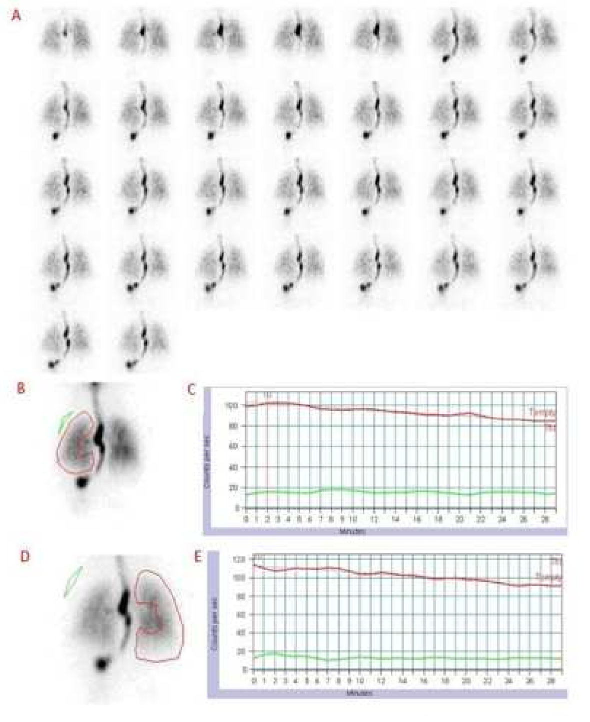

Figure 12: 58 year old female diagnosed with diabetes mellitus for 12 years, developed neuropathy and retinopathy 6 years back and currently on oral insulin therapy. Tc-99m DTPA aerosol lung scintigraphy, dynamic images (A) showed aerosols in bilateral lungs. ROI (B) of left lung and TAC (C) of left lung showing the clearance pattern. ROI (D) of right lung and TAC (E) of right lung showing the clearance pattern. $T_{1/2}$ of the left lung is 78 minutes and right lung is 74 minutes.

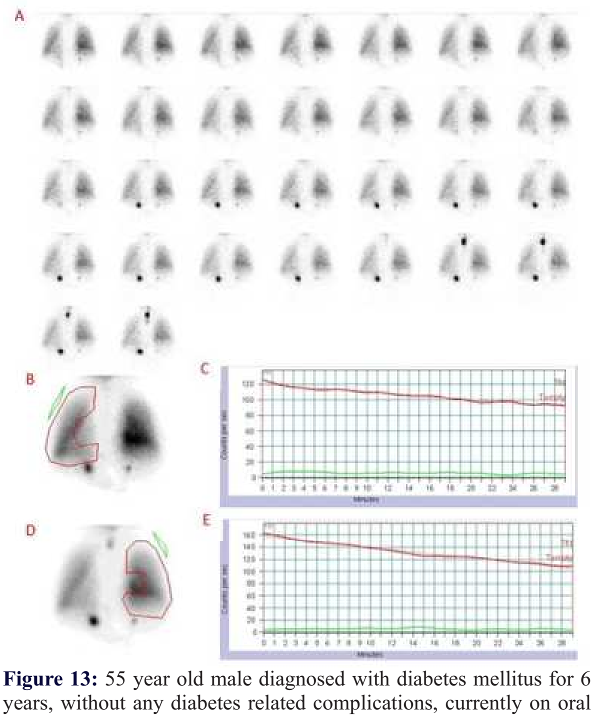

Figure 13: 55 year old male diagnosed with diabetes mellitus for 6 years, without any diabetes related complications, currently on oral hypoglycaemic agents. Tc-99m aerosol lung scintigraphy, dynamic images (A) showed the aerosols in bilateral lungs and the stomach. Mild contamination was noted inferior to right lung. ROI (B) of left lung and TAC (C) of the left lung showing the clearance pattern. ROI (D) of the right lung and TAC (E) of the right lung showing the clearance pattern. $T_{1/2}$ of the left lung is 56 minutes and the right lung is 42 minutes.

DISCUSSION:

In our study, we performed Tc-99m DTPA aerosol lung scintigraphy in 28 healthy non-smoking volunteers, and the mean clearance $T_{1/2}$ in them was 47.64 ±12.72 minutes. Timur Pirildar et al. performed Tc-99m DTPA aerosol scintigraphy in 13 healthy non-smokers as a part of their study, where they intended to assess the alveolar epithelial permeability in patients suffering from Sjogren's syndrome. The mean half-time clearance in them was 42.32 ± 13.28 minutes, which is slightly lower when compared to our study (47.64 ± 12.72 minutes).[12] Fikriye G et al. evaluated 15 healthy non-smoking people as a part of their study in the assessment of impairment of alveolar epithelial permeability in Behcet's disease with Tc-99m DTPA aerosol scintigraphy. The mean half-time clearance in them was 46.53 ± 22.41minutes, which is similar to our study (47.64 ± 12.72 minutes).13 Eser kaya et al. performed Tc-99m DTPA aerosol scintigraphy in 6 healthy non-smoking volunteers as a part of their study to look for a change in alveolar permeability in welders.[14] The mean clearance $T_{1/2}$ was 48.1 ± 9.7 minutes, which was similar to of our study (47.64 ± 12.72 minutes).

A.M Samuel et al. performed Tc-99m DTPA aerosol lung scintigraphy in 52 healthy Indian non-smoking volunteers as a part of their study to evaluate the effect of radioiodine therapy on the pulmonary capillary membrane. This was the Indian study conducted in Radiation Medicine Centre, Mumbai.[15] The mean Tc-99m DTPA clearance half-time value for the healthy volunteers was 50.5 ± 17.6 minutes, which is almost similar to the mean value of our study (47.64 ± 12.72 minutes).

J.G. Jones et al. performed a pilot study in 5 healthy volunteers, among them 2 were non-smokers and the mean half-time clearance in them was 59 minutes which was slightly higher when compared to our study (47.64 ± 12.72 minutes).[16] Similarly,Clare Beadsmoore et al. also performed Tc-99m DTPA aerosol scintigraphy in 10 healthy non-smoker volunteers as a part of their study, and the mean Tc-99m DTPA clearance half-time was 80.3 ± 20 minutes which was higher than our study (47.64 ± 12.72 minutes).[17]

Dalcin et al. performed aerosol lung scintigraphy using Tc-99m DTPA aerosols in 30 healthy volunteers as a part of their study to compare the clearance half time in SLE patients with a normal population. The mean Tc-99m DTPA clearance half-time was 85.87 minutes (range 78.85-92.87 minutes), which is more than our study (47.64 ± 12.72 minutes).[18] Piga M et al. evaluated 10 non-smoking subjects as a part of their study to compare the clearance half time of Tc-9m DTPA in Scleroderma patients with healthy subjects. The mean Tc-99m DTPA clearance half-time was 105± 14 minutes which is higher than our mean value (47.64 ± 12.72 minutes).[19]

Sibel Guldekin et al. did aerosol lung scintigraphy in 35 participants, in which 19 were hyperthyroid patients and 16 were healthy volunteers.[20] The mean half-time clearance was 149.1 + 79.2 minutes in the hyperthyroid group and 172.1 ± 83.0 minutes in the volunteer group. The mean $T_{1/2}$ of 172.1+ 83.0 minutes in healthy volunteers was higher when compared to our study (47.64 ± 12.72 minutes).

The variations in the mean clearance values among different studies can be attributed to the differences in participant selection, age of the participants, geographical variations of the population, scan acquisition parameters and the selection of the region of interest. Some studies acquired planar images with a single- headed gamma camera, and they acquired dynamic images in the posterior view only.[12,19,20] The region of interest selected in our study excludes the central area to avoid the interference of large airways, whereas some studies used whole lung ROI and some used only peripheral third of lung parenchyma.[12,20]

Biray Caner et al. did a similar kind of study, in which they tried to study the impaired lung epithelial permeability in diabetic patients. They recruited a total of 53 participants (20 healthy volunteers and 33 diabetic patients). Out of 33 diabetic patients, 13 patients had diabetes related complications like neuropathy, retinopathy, and nephropathy.[21] Tc-99m DTPA aerosol lung scintigraphy was performed in all the participants. The mean Tc-99m DTPA clearance $T_{1/2}$ in the healthy volunteers was 91.97 ± 18.21 minutes, which is higher than 47.64 ± 12.72 minutes of our study. The mean Tc-99m DTPA clearance $T_{1/2}$ value in diabetic patients without complications was 93.67 ± 21.23 minutes, and the mean Tc-99m DTPA clearance $T_{1/2}$ value in diabetic patients with complications was 133.05 ± 46.97 minutes. They found a significant difference in mean between diabetic patients with complications and those without complications ($p < 0.005$), and diabetic patients with complications and healthy volunteers ($p < 0.005$), but they did not find any significant difference in mean between healthy volunteers and diabetic patients without complications ($p > 0.05$). We also compared in a similar manner, where the mean clearance $T_{1/2}$ in diabetic patients without complications was 51.38 ± 14.35 minutes and the mean clearance $T_{1/2}$ and in diabetic patients with diabetes related complications was 61.04 ±15.28 minutes. This difference in the values of mean clearance $T_{1/2}$ may be due to various factors as discussed earlier, but in both the studies, there is a significant difference in the mean clearance $T_{1/2}$ between diabetic patients with complications and those without complications, and diabetic patients with complications and healthy volunteers. In a similar manner, there is no significant difference in mean $T_{1/2}$between healthy volunteers and diabetic patients without complications in both studies.This suggests that there is a significant decrease in lung epithelial permeability in diabetic patients who have diabetes related complications. The complications that were observed in both the studies were due to the damage of microvasculature. As lungs have extensive microvasculature to accommodate the entire cardiac output, there is a high probability of microvasculature involvement. However, this may not be clinically evident due to significant pulmonary microvascular reserve. But it has a high tendency to exacerbate the damage to lung parenchyma due to any other pathology.

In our study, we found more than 6 minutes difference between the clearance half-time of two lungs of the same individual in six participants. Among them, 5 were diabetic patients and 1 was a healthy volunteer. We did not find any structural changes in lung parenchyma in NCCT of the thorax in any of the diabetic patients. This difference may be due to the presence of an underlying occult disease process or merely physiological.

Contrary to the study done by Biray Caner et al., K Mousa et al. showed that there is no significant difference in Tc-99m DTPA clearance in diabetic patients with and without complications. They studied 50 non-insulin dependent diabetic mellitus patients aged between 40-70 years. Out of 50, 31 were diabetic-related complications and 19 did not have any diabetes related complications. The mean Tc-99m DTPA clearance $T_{1/2}$ was 73.35 ± 26.06 minutes and 75.17 ± 21.85 minutes in patients with and without complications, respectively, which is not in agreement with our study.[38(22)] K Mousa et al. suggested that this absence of significant difference in the clearance half-times in diabetic patients with and without complications can be due to a low sample size. However, when compared to the data from the normal population from their institute, they found a significant increase in mean clearance $T_{1/2}$ in diabetic patients, which is agreeing with our study.

Kemal Ozyahin et al. found significantly reduced lung epithelial permeability in type 2 diabetes mellitus patients, similar to our study.[23] They evaluated 40 participants, out of which 25 were diagnosed cases of diabetes and 15 were healthy controls. Among 25, 23 had diabetes related microvascular complications. They performed DLCO and Tc-99m DTPA aerosol lung scintigraphy in all participants. The mean Tc-99m DTPA clearance $T_{1/2}$ was 112.7 ± 37.8 and 84.6 ± 29.7 minutes in diabetic patients and healthy controls respectively, which are higher when compared to our study (55.71 ± 15.42 and 47.64 ± 12.72 minutes, respectively). However, the difference in the mean values is significant ($p < 0.05$), which is similar to our study. DLCO values did not show any significant difference between disease and control groups.

The major pathological change in diabetes related microangiopathic complications is the thickening of the basement membrane. The thickening of the basement membrane starts early in the disease process and increases with the duration of diabetes, which is in turn reflected in ventilation functions. We analysed mean clearance half-times in the diabetic patients according to their duration of diabetes. The mean clearance $T_{1/2}$ is higher in diabetic patients with duration of disease for more than 10 years (61.00 ± 15.43 minutes) when compared with those who are suffering with diabetes for less than 10 years (53.21 ± 15.28 minutes), and it was statistically significant ($p = 0.01$). Kemal Ozyahin et al. also observed similar findings where they divided the diabetic population into two groups, those who had diabetes for less than 5 years ($n = 6$) and those who had it for more than 5 years ($n = 19$).[23] The mean clearance $T_{1/2}$ was 93.5 ± 29.9 minutes and 118.8 ± 38.7 minutes in patients with diabetes for less than 5 years and more than 5 years of duration, respectively, which was significant ($p < 0.05$). They did not find any significant difference in the mean clearance between healthy volunteers (84.6 ± 29.7 min) and diabetic patients with duration of diabetes less than 5 years (93.5 ± 29.9). But the difference in mean clearance $T_{1/2}$ is significant (p = 0.006) when compared with diabetic patients with duration of diabetes more than 5 years (118.8 ± 38.7 minutes). Similarly, our study also did not find any significant difference in the mean clearance $T_{1/2}$ between healthy volunteers (47.64 ± 12.72 minutes) and diabetic patients with duration of diabetes less than 10 years (51.74 ± 14.81 minutes). But the difference in mean clearance $T_{1/2}$ is significant (p = 0.003) when compared with diabetic patients with duration of diabetes more than 10 years (61.33 ± 14.78 minutes). This suggests that the duration of diabetes also plays an important role, with damage to lung epithelium increasing with the duration of diabetes.

In our study, we found a higher mean clearance $T_{1/2}$ in diabetic patients who are being treated with insulin (59.76 ± 14.72 minutes), when compared with those who are being treated with oral hypoglycaemic agents (52.64 ± 15.44 minutes). However, the difference is not statistically significant (p = 0.08). Most of the patients who are on insulin therapy had diabetes related complications. The reason for management with insulin in most of these cases is poor hypoglycaemic control with oral agents. In cases with poor hypoglycaemic control, there is an increased possibility of diabetes related pulmonary epithelial complications, which may have resulted in slow clearance of Tc-99m DTPA aerosols.

Our study, similar to most of these studies, showed a significant increase in Tc-99m DTPA clearance half-times in diabetic patients when compared to a healthy population, which is due to decreased epithelial permeability in those with diabetes. In view of evolving availability of inhalational insulin preparations for diabetic patients, performing a Tc-99m DTPA aerosol lung scintigraphy before starting the therapy may be useful in assessing lung epithelial permeability, as it plays an important role in absorption of the inhaled insulin.

CONCLUSION:

With this study, we are concluding that there is an impaired lung epithelial permeability in diabetic patients, especially in those who had diabetes related complications and who had diabetes for a longer duration.

With this study, we can also assume that Tc-99m DTPA aerosol lung scintigraphy can detect the changes in epithelial permeability in diabetic patients before they are even symptomatic.

Strengths And Limitations: Strengths Of The Study:

- To our knowledge, this is the first study that was conducted in Indian diabetic patients by using Tc-99m DTPA aerosol scintigraphy.
- As a part of the study, Tc-99m DTPA aerosol scintigraphy was performed even in healthy volunteers. To our knowledge, this is the first study that is conducted in healthy volunteers in the south Indian population, the clearance half-time values obtained from our study may be useful for similar studies in the future.

Limitations Of The Study:

- Because of the difficulty in recruiting healthy volunteers, diabetic patients and healthy volunteers were considered in a 2:1 ratio instead of 1:1 ratio at the time of sample calculation.
- Most of the participants were females, as we included only non-smokers for the purpose of study.
- Tc-99m DTPA clearance half-times could not be compared with pulmonary function tests and DLCO as the latter studies were not performed.

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Conflicts Of Interest: There are No conflicts of interest.

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