Effect of glycemic state on ventilatory lung functions in asymptomatic current smokers

Heba H Eltrawy, Samiha M Abo-Bakr, Rania A Abdelraoof, Inass H Ahmad

Abstract

Objective: The association of smoking with glycemic level may suggest long term effects that may lead to airways obstruction. We aimed to study the effect of glycemic state on lung functions in asymptomatic current cigarettes smokers.

Methods: This observational cross sectional study was conducted on 100 asymptomatic current cigarette smokers. Data regarding age, sex, smoking history including age of onset, smoking index and smoking duration were taken. Spirometric-indices (VC%, FVC%, FEV1%, FEV1/FVC ratio, FEF25-75%), Serum fasting plasma glucose mg/dl (FPG) and glycated hemoglobin% (HbA1C%) were measured.

Results: Spirometric-indices were significantly lower in smokers with pre DM and DM compared to those with no DM ($p < 0.05$). Frequencies of large and small airways obstruction were significantly higher in smokers with pre DM and DM compared to those with no DM ($p < 0.05$). Multivariate linear regression analysis revealed that HbAIC and FBG mg/dl values were predictive factors for decreased FEV1/FVC ($p=0.001$, $B=1.202$), ($p=0.03$, $B=-0.068$) respectively and decreased FEF 25-75% ($p<0.001$, $B=-2.196$), ($p<0.001$, $B=0.158$) respectively.

Conclusion: Lower spirometric indices in smokers with DM and pre-DM compared to smokers with no DM support the relationship between COPD and DM. The increased HbA1C and FBS level among smokers are predictors of both large and small airways obstruction ($p < 0.05$).

Keywords: Smoking; Pulmonary function tests; Glycosylated hemoglobin; Diabetes.

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Introduction

Numerous components of tobacco smoke are documented to be related to decreased insulin sensitivity in humans, concerning smoking with insulin resistance. However, the mechanisms responsible for this remain unclear, thus, tobacco smoking has been considered an important risk matter for the presence of insulin resistance and eventually type 2 diabetes mellitus (DM)[1].

Association between cigarette smoking and the increased HbA1C may be related to the nicotine, which has been established to increase plasma levels of catecholamines, which raise hepatic glycolysis and gluconeogenesis. Catecholamines might reduce the number of insulin binding sites in addition to reduced synthesis of glucose transporters [2].

The current body of evidence suggests that the lung is one of the targeted organs in the multisystem affection that is seen in DM; due to presence of lung micro-vasculatures and plentiful connective tissue in the lung. Secondly, DM is a common comorbidity of COPD[3].

Materials and Methods

This cross sectional study was carried out over the period from January to June 2020 at Department of Pulmonology, Al-Azhar University, Faculty of Medicine for Girls, Egypt.

Study population

The study was conducted on 100 asymptomatic current smokers classified into three groups, diabetic group, prediabetic group, and non-diabetic group.

Exclusion criteria

Individuals with known chest diseases, DM or chronic diseases (liver or kidney or gum disease, H. pylori infection) were also excluded from the study as they cause elevation of HbA1C.

1- Complete history was taken including age, sex, age of smoking onset, number of smoked cigarette per day and smoking interval. The smoking index (pack/year) was calculated as a number of packs smoked daily multiplied by number of years of smoking. The body mass index (BMI) was calculated as [weight (kg)/height (m) 2].

2- Complete blood count and routine labs were done to exclude patients with chronic diseases that affect HbA1C level.

3- Venous blood sample was taken after an 8 hour overnight fasting for measurement of HbA1C% and fasting plasma glucose mg/dl (FPG) levels. Studied members were categorized into three groups based on either FPG mg/dl [No DM (<100 mg/dl), pre-DM (100-125 mg/dl) and DM (≥126 mg/dl)] and/or HbA1C [no DM (< 5.7%), pre-DM (5.7-6.4%), and DM (≥6.5%)] [4].

4- Spirometry was carried out using SPIROSIFT SP-5000, (Japan). The following spirometric-indices were assessed by three re-

peated procedures, as recommended by ERS (5): vital capacity (VC%predicted), forced vital capacity (FVC% predicted), forced expiratory volume in the first second (FEV1%predicted), FEV1\FVC ratio, and forced expiratory flow rate 25-75 (FEF25-75%predicted). To assess the frequencies of obstructive pattern, the study participants were classified based on FEV_1\FVC ratio into: 1) large airway obstruction (FEV_1 \FVC<70%), 2) No large airway obstruction (FEV_1/FVC) ≥70%. They were also classified based on FEF 25-75% into: 1) Small airways obstruction (FEF 25-75%<65), and 2) No small airways obstructions (FEF 25-75% ≥65).

Figure 1: *Bar chart showing Comparison of Spirometric-indices between smokers with no DM, smokers with pre DM and DM (based on HbA1C)*

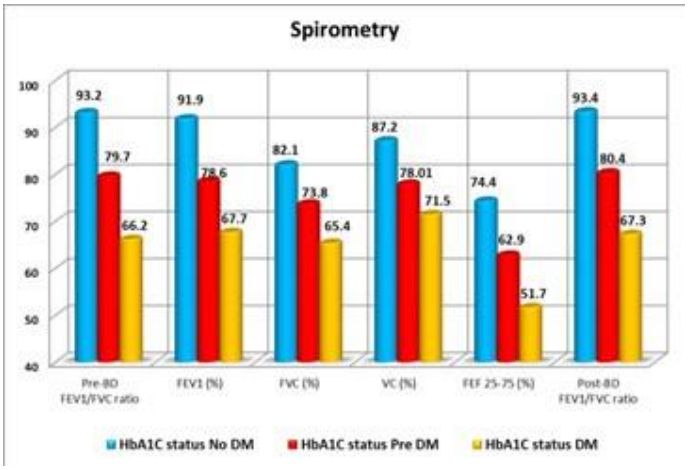
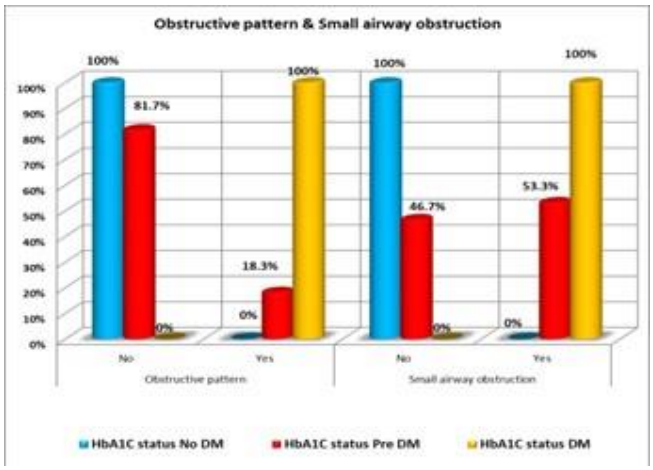


Figure 2: *Bar chart showing Comparison of (large airway obstruction and Small airway obstruction frequencies between smokers with no DM, pre DM and smokers with DM (based on HbA1C).*



Ethical consideration

The research protocol was approved by Faculty of Medicine for Girls, Al-Azhar University institutional review board (IRB No.202001027), Cairo, Egypt (ethical review committee). Sharing was voluntary; an informed written agreement was obtained from each participant before enrolment into the study. Data were anonymous and coded to assure confidentiality of participants.

Statistical analysis

We employed descriptive statistics (mean±standard deviation for quantitative data and frequencies for categorical data) to present the collected data. The hypothesize of significant association between continuous variables was examined using Independent-samples t-test or One-way ANOVA, when comparing two and three groups, respectively. The hypothesize of significant association between categorical variables was examined using Chi-square (x2) test. We examined potential predictors of large airway obstruction using binary logistic regression. The null hypothesize was rejected at p-value of less than 5%. Analysis of recorded data was done by using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Table 1 showed descriptive data of studied smoker group.

Table 2, Figure 3 showed that the spirometric-indices were significantly lower in smokers with pre DM and DM compared to those with no DM, and in smokers with DM compared to those without DM ($p < 0.05$). On the other hand, FBS was significantly higher in smokers with pre DM and DM compared to those with no DM, and in smokers with DM compared to those without DM ($p<0.05$).

Table 3, Figure 2 revealed that the frequencies of large airway and small airways obstruction were significantly higher in smokers with pre DM and DM compared to those with no DM ($p< 0.05$).

Table 4 shows that HbA1C ($p=0.001$, B=1.202), FEF 25-75% ($p=0.002$, B=0.292), post-BD FEV_1/FVC ratio ($p<0.001$, B=0.749), smoking duration ($p=0.041$, B=- 0.131), and lastly FBS ($p=0.03$, B=- 0.068) were predictive factors of large airway obstruction (by multivariate regression analysis) (FEV_1/FVC<70) among smokers.

Table 5 demonstrates that that HbA1C ($p<0.001$, B=-2.196), FVC% ($p<0.001$, B=0.705), VC% ($p=0.036$, B=0.357), pre-BD FEV_1/FVC ratio ($p=0.002$, B=-0.354), and lastly FBS ($p<0.001$, B=0.158) were the predictive factors for small airways obstruction (FEF25-75% <65%) in smokers by multivariate regression analysis.

Tables 1: *Descriptive data of the studied asymptomatic current smokers*

Demographic data		**Smokers (N = 100)**
Age/yrs	Mean ± SD	41.59 ± 13.52
Sex	Male	87 (87%)
	Female	13 (13%)
BMI (kg/m2)	Mean ± SD	26.66 ± 3.16
Age of starting smoking/yrs	Mean ± SD	24.44 ± 8.88
Smoking duration/ yrs	Mean ± SD	29.18 ± 10.94
Smoking index (pack/year)	Mean ± SD	22.82 ± 9.37
FEV1/FVC ratio	Mean ± SD	81.54 ± 9.72
FEV1%	Mean ± SD	80.67 ± 8.71
FVC%	Mean ± SD	74.63 ± 5.79
VC%	Mean ± SD	79.28 ± 5.82
FEF25-75%	Mean ± SD	64.55 ± 7.75
FPG mg/dl	Mean ± SD	107.26 ± 16.29
HbA1C%	Mean ± SD	5.89 ± 0.72

Tables 2: *Comparison of Spirometric-indices between smokers with no DM, smokers with pre DM and smokers with DM (based on HbA1C)*

Spirometry data		based on HbA_1C	based on HbA_1C	based on HbA_1C	Test$^{\beta}$	Post hoc analysis	Post hoc analysis	Post hoc analysis
		No DM	Pre DM	DM		P1	P2	P3
		(N = 30)	(N = 60)	(N = 10)				
Pre-BD FEV1/FVC ratio	Mean ±SD	93.2 ± 2.5	79.7 ± 6.7	66.2 ± 0.7	0.001	0.002	0.001	0.003
FEV1 %	Mean ±SD	91.9 ± 2.2	78.6 ± 5.5	67.7 ± 0.9	0.001	0.001	0.001	0.001
FVC %	Mean ±SD	82.1 ± 2.2	73.8 ± 3.4	65.4 ± 1.7	0.v002	0.003	0.001	0.001
VC %	Mean ±SD	87.2 ± 2.1	78.01 ± 3.6	71.5 ± 1.01	0.001	0.003	0.003	0.001
FEF25-75 %	Mean ±SD	74.4 ± 3.1	62.9 ± 4.09	51.7 ± 1.9	0.003	0.002	0.001	0.001
Post-BD FEV1/FVC ratio	Mean ±SD	93.4 ± 2.5	80.4 ± 6.1	67.3 ± 0.4	0.001	0.002	0.001	0.003
FBS mg/dl	Mean ±SD	88.3±5.9	113.1±7.9	136.6±4.5	0.001	0.004	0.001	0.001

β: ANOVA, P1: no DM vs. pre DM, P2: no DM vs. DM, P3: pre DM vs. DM

Abbreviations: yrs: years, FVC: forced vital capacity, FEV1: forced expiratory volume in first second and FEF25-75 %: forced expiratory volume in 25-75% of vital capacity, BD: bronchodilators, HbA1C: glycosylated hemoglobin, FPG: fasting blood sugar

Tables 3: *Comparison of frequencies of large airway and small airways obstruction between smokers with no DM, smokers with pre DM and smokers with DM (based on HbA1C)*

					Test*	Chi-square test		
		No DM	Pre DM	DM		P1	P2	P3
		(N = 30)	(N = 60)	(N = 10)				
large airway obstruction	Non obstructive	30 (100%)	49 (81.7%)	0 (0%)	0.001	0.012	0.001	0.002
	obstructive	0 (0%)	11 (18.3%)	10 (100%)				
Small airway obstruction	Non obstructive	30 (100%)	28 (46.7%)	0 (0%)	0.002	0.001	0.003	0.005
	obstructive	0 (0%)	32 (53.3%)	10 (100%)				

*: Chi-square P1: no DM vs. pre DM, P2: no DM vs. DM, P3: pre DM vs. DM

Abbreviations: DM: diabetes mellitus, pre DM: pre diabetes mellitus

Tables 4: *Multivariate linear regression analysis for predictive factors of large airway obstructive pattern (FEV1/FVC < 70%)*

FEV_1/FVC ratio	B	SE	P	95% CL	
(Constant)	16.361	16.562	0.326	-16.56	49.29
Age/yrs	-0.001	0.008	0.873	-0.018	0.015
Sex	0.112	0.297	0.706	-0.478	0.702
Weight/ kg	0.001	0.018	0.965	-0.035	0.037
BMI	0.011	0.055	0.845	-0.099	0.121
Smoking index	0.01	0.079	0.897	-0.148	0.168

Smoking duration/ yrs	-0.131	0.063	0.041	-0.258	-0.005
Age of smoking onset/yrs	-0.129	0.07	0.067	-0.268	0.009
FEV1%	0.158	0.144	0.275	-0.128	0.444
FVC%	-0.026	0.171	0.877	-0.365	0.313
VC%	-0.243	0.154	0.118	-0.548	0.063
FEF25.75%	0.292	0.093	0.002	0.107	0.477
Post BD FEV1/FVC ratio	0.749	0.064	0.001	0.622	0.876
FBS mg/dl	-0.068	0.031	0.03	-0.13	-0.007
HbA1C	1.202	0.341	0.001	0.525	1.879

B: Regression coefficient, SE: Standard error, CL: Confidence interval.

Abbreviations: BMI: body mass index yrs: years, FVC: forced vital capacity, FEV1: forced expiratory volume in first second and FEF25-75 %: forced expiratory volume in 25-75% of vital capacity, HbA1C: glycosylated hemoglobin, FPG: fasting blood sugar.

Tables 5: *Multivariate linear regression analysis for predictive factors of decreased FEF25-75% (small airway obstructive pattern).*

FEF 25 – 75%	**B**	**SE**	**P**	**95% CL**	
(Constant)	-51.716	17.46	0.004	-86.43	-16.992
Age/yrs	-0.002	0.009	0.798	-0.021	0.016
Sex	-0.223	0.326	0.495	-0.872	0.425
Weight /kg	0.019	0.02	0.344	-0.021	0.058
BMI	-0.055	0.061	0.372	-0.175	0.066
Smoking Index	0.083	0.087	0.341	-0.09	0.257
Smoking duration/ yrs	0	0.072	0.997	-0.143	0.142
Age of starting smoking /yrs	0.046	0.078	0.559	-0.109	0.201
Pre.BD FEV1/FVC ratio	0.354	0.113	0.002	0.129	0.579
FEV1%	0.168	0.158	0.292	-0.147	0.483
FVC%	0.705	0.172	0.001	0.364	1.046
VC%	0.357	0.167	0.036	0.024	0.689
Post BD FEV1/FVC ratio	-0.172	0.112	0.128	-0.395	0.051
FBS mg/dl	0.158	0.031	0.001	0.097	0.219
HbA1C	-2.196	0.323	0.001	-2.839	-1.553
B: Regression coefficient, SE: Standard error, CL: Confidence interval. Abbreviations: BMI: body mass index ,yrs: years, FVC: forced vital capacity, FEV1: forced expiratory volume in first second and FEF25-75 %: forced expiratory volume in 25-75% of vital capacity, HbA1C: glycosylated hemoglobin, FPG: fasting blood sugar.					

*: Chi-square test, *: significant test

Abbreviations: BMI: body mass index yrs: years, FVC: forced vital capacity, FEV1: forced expiratory volume in first second and FEF25-75%: forced expiratory volume in 25-75% of vital capacity, HbA1C: glycosylated hemoglobin, FPG: fasting blood sugar

Discussion

The relationship between DM and lung function remains essential because of potential epidemiological and clinical consequences. May systemic inflammation of DM clarify the affected lung function?[4-6] In the current study all smokers with DM (100%) had large airway obstruction and small large and small airway obstruction in PFT, while only 18.3% and 53.3% of smokers with pre-DM had large and small airways obstruction respectively, on the other hand no smokers without DM had abnormal PFT (Table 3). These results support the possible involvement of in- flammatory process in diabetic patients, which subsequently can progress to chronic airway obstruction. The association of smoking with HbA1c recommends long term effects that may lead to higher risk of airways obstruction which is a feature of COPD.[7] The mechanisms that cause high prevalence of DM in COPD is still indistinct; however, the existence of inflammatory process,

as well as hypoxic injuries and oxidative stress, may represent potential. Systemic mechanisms of the high COPD prevalence in diabetic patients is prevalent in the setting of COPD and T2DM sharing character to both COPD and to T2DM, which initiates insulin resistance, atherosclerosis and many systemic expressions of COPD.[8]

These mechanisms are supported by many observations. For example, Sagun et al. (2015)[9] demonstrated significant elevation in the prevalence of lung dysfunction in patients with insulin resistance of group (p=0.039). Baba et al. (2017)[10] reported that the prevalence of obstructive ventilatory function pattern was significantly more common among patients with impaired glucose tolerance and smokers. Tina et al. (2016)[7] reported that 48.3% of persons with T2DM had smoking history with 46.2 pack years, and current smokers were 20.9%, twenty percent of them had normal PFT and one-third had COPD. Additionally, 74% had variable degrees of obstructive pattern (p<0.001). Kinney and Baker (2014) recorded that persons with DM have a 22% in- creased danger of developing COPD.[11] The mechanisms under- lying this reduction in spirometric indices in patients with pre- DM or DM are not fully clear; however, various theories were proposed including significant increase in the alveolar epithelial thickness and microangiopathy within the lung. Besides, pa- tients with DM may exhibit reduced recoiling capacity of the lung, leading to impaired volumes and recoil. In return, the ex- halation function is impaired.[12] However, common mechanisms, which are believed to contribute to lung dysfunction in diabetic patients, include microvascular abnormalities, glycosylation of tissue proteins, and abnormal respiratory muscle function secondary to autonomic neuropathy.[13] It was also reported that lung function starts to deteriorate in early stage of T2DM, even before the disease become symptomatic or develop complications; thus, it was proposed that impaired lung function is developed before the onset of T2DM, resembling the pathogenesis of endothelial dysfunction in diabetic patients.[8] Tesema et al. (2020) recorded that there were significantly decreased in force volume parameters among T2DM patients, compared to healthy population. Same results of reduction of spirometric indices in patients with DM were reported in previous studies.[14,15,16] Baba et al. (2017)[10] reported that HbA1C ≥5.6% was closely associated with impaired FEV1/FVC. Earlier studies demonstrated lower FEV1 and FVC in diabetic patients than normal population. However FVC decrease was more reliable than FEV1, suggesting a restricting pattern.[17] A meta-analysis study indicated that lung function is affected in patients with DM and pre-DM compared to members with normal FBS level, also Davis et al. (2004) in Fremantle Diabetes study reported that the reduction of FEV1, FVC, PEF and VC was predicted by poor glycemic control. [18,19] One percent increment of HbA1C was associated with 4% decrement of FEV1 and 6% decrease of FVC. Our results were not in agreement with Jamatia et al. (2014)[6] The FVC, FEV1, PEFR and FEF25-75% were decreased while FEV1/FVC was increased in patients with T2DM when compared to the controls with larger reduction in FVC than FEV1. The consequent larger FEV1/FVC ratio suggested restrictive physiology. The higher HbA1C and FBS, among smokers are predictors of both large and small airways obstruction (p <0.05) (Tables 4 and 5). Similarly, Chen et al. (2013) reported that DM was a considerable risk factors for small airways obstruction (OR=2.25; p 0.039).[20] Baba et al. (2017)[10] multivariable logistic regression was performed to estimate the risk of FEV1/FVC <70%, it revealed that age (≥60 years), HbA1C levels (≥ 5.6%), current smoking, and previous smoking were significantly associated with a FEV_1/FVC <70%. Also the respiratory system seems to be a target organ for diabetic patients as regard pulmonary functions results.

Conclusion

Current across sectional study confirms the association between reduced PFT and glycemic state in asymptomatic current smokers. Smoking was associated with preclinical or asymptomatic reduction of spirometric-indices and higher HbA1C levels in a sample of Egyptian current smokers who were non-COPD and non-diabetic adult males. Increased HbA1C and FBS among smokers are predictors of both large and small airways obstruction (p<0.05).

Limitation of Study

The limitations of our research are that it was a single center study so the results cannot be generalized. The smokers differ widely in their smoking manner, making quantitation of the nicotine dose absorbed by an individual smoker and from an individual cigarette are difficult.

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