A study of the relationship between pulmonary function tests and both fasting plasma glucose and glycated hemoglobin levels among asymptomatic cigarette smokers
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\textbf{Background} Tobacco smoke has been recognized as an independent risk factor for chronic obstructive pulmonary disease and diabetes mellitus type 2.

\textbf{Aim} To investigate the association between the presence of airflow obstruction in pulmonary functions and both fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels among asymptomatic cigarette smokers.

\textbf{Patients and methods} Pulmonary function indices via spirometry and both FPG and HbA1c levels were altogether assessed in 300 apparently healthy participants attending health checkup clinic. Participants were stratified according to their smoking status into group I, which included 150 current and former cigarette smokers (ever smokers), and group II, which included 150 participants with no history of smoking (never smokers).

\textbf{Results} FPG and HbA1c\% were significantly higher among group I compared with group II (P=0.001 and 0.002, respectively). However, percent of forced expiratory volume in 1 s/forced vital capacity ratio less than 70% was statistically more prevalent among group I compared with group II (17.3, 6.7\%, respectively, P=0.042), and the odds ratio (OR) of its occurrence increased with FPG more than or equal to 100 mg/dl [OR=2.91; 95\% confidence interval (CI)=1.62–4.01], HbA1c more than or equal to 5.6\% [OR=2.07; 95\% CI=0.12–0.77], age more than or equal to 50 years (OR=2.85; 95\% CI=1.69–3.99), smoking index more than or equal to 25 pack-years (OR=3.11; 95\% CI=1.85–3.66), and BMI more than or equal to 25 kg/m\textsuperscript{2} (OR=2.33; 95\% CI=0.06–0.84).

\textbf{Conclusion} Risk of chronic obstructive pulmonary disease is increased among asymptomatic current or former cigarette smokers, especially elderly with impaired glucose homeostasis.

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\textbf{Keywords:} chronic obstructive pulmonary disease, cigarette smoking, diabetes mellitus, fasting plasma glucose, glycated hemoglobin, pulmonary function tests

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\section*{Introduction}
Tobacco smoke is a major cause of preventable morbidity and mortality worldwide. Nicotine, one of the many components of tobacco smoke, is established to be associated with decrease in the sensitivity of insulin in humans, linking smoking with insulin resistance. However, the mechanisms responsible for this remain unclear, and hence, cigarette smoking has been considered an important risk factor for the development of insulin resistance and ultimately type 2 diabetes mellitus (DM) [1].

Furthermore, tobacco smoke is also the commonest risk factor for chronic obstructive pulmonary disease (COPD) worldwide [2], which is a disease known to affect the quality of life significantly [3] as it increases the annual decline rate in forced expiratory volume in the first second (FEV\textsubscript{1}) and overall, leading to increased mortality and morbidity compared with nonsmokers [4].

The current understanding of the pathophysiology of COPD is that smoking causes the release of cytokines, namely, tumor necrosis factor alpha soluble receptor, interleukin-1, and interleukin-6, all of which upregulate the activity of neutrophil and macrophage and consequently initiate a cascade of systemic inflammation [5,6]. Strikingly, these mediators have also been postulated to play a role in developing insulin resistance in muscle and liver tissue, which consequently increases the likelihood of future development of DM [7]. Cigarette smoking-related systemic inflammation is therefore hypothesized as the joint etiology independently influencing both lung function and glycemia [8,9].

Several large-scale western studies have linked COPD to DM, an example of which is an American study conducted on 47 million people investigating the prevalence of COPD-associated comorbidities, and it concluded that DM is significantly prevalent in patients with COPD [10].
On the contrary, research into the association between diabetes and pulmonary function in diabetic subpopulation free from overt pulmonary disease has resulted in inconsistent outcomes among studies. A recent meta-analysis on 40 studies attempted to characterize pulmonary function in such population compared with normoglycemic participants and concluded that impaired pulmonary function, but of the restrictive pattern, is the most frequently encountered pattern [11].

However, another study analysis of a large Japanese cohort (follow-up period up to 2 years) suggested that low lung volume might in fact be a risk factor for impaired glucose tolerance rather than impaired fasting glucose (IFG), but an association between prediabetes and early stages of COPD could not be found [12].

The aim of the current study was to investigate the association between prevalence of airflow obstruction as reflected in pulmonary function tests measured via spirometry and two markers that define glycemic status, namely, fasting plasma glucose (FPG) levels and glycated hemoglobin concentration (HbA1c%) among asymptomatic cigarette smokers.

Patients and methods
This is a prospective observational study enrolling 300 participants, aged 40 years or older, attending the health checkup clinic at Nasr City Police Hospital during the period between April 2017 and April 2018. Participants were grouped into two groups based on their smoking status: group I, which included 150 apparently healthy cigarette smokers (whether current or former) (ever smokers group) as the study group, and group II, which included 150 never smokers matched for as a control group (never smokers group). Smoking status is defined by the Centers for Disease Control and Prevention, where current smoker is the one who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes, and former smoker is the one who has smoked 100 cigarettes at least in his or her lifetime but who had quit smoking, whereas a never smoker is the one who has never smoked or has smoked less than 100 cigarettes in his or her lifetime. Cumulative exposure to tobacco smoke was also quantified via calculation of the smoking index (SI) defined as number of cigarette packs smoked a day for a year (pack-years) [13].

Exclusion criteria
Any individual with physician-diagnosed airway disease and patients known to be on antidiabetic medication (insulin and/or oral hypoglycemic therapy) to avoid bias related to drug-induced effects on glycemic markers were excluded.

All enrolled participants were subjected to full history taking (with emphasis on detailed smoking history regarding duration and amount of cigarettes smoked per day) and physical examination, including BMI, which was calculated as person’s weight in kilograms/square the height in meters (kg/m²), where 18.5–24.9 kg/m² was considered normal/healthy body weight and 25 kg/m² or more was the reference point for overweight according to Centers for Disease Control and Prevention [14].

Laboratory investigations
Venous blood samples were collected after 12 h of fasting and measured via automatic clinical chemistry analyzer. FPG levels were measured by enzymatic methods. High-performance liquid chromatography was used to assess HbA1c following the National Glycohemoglobin Standardization Program protocol [15].

Serum FPG level of 100 mg/dl or more was taken as a cutoff value to indicate IFG, a category of intermediate hyperglycemia, whereas HbA1c concentrations of 5.6% or higher was taken as a cutoff value to reflect chronic hyperglycemia. Both are glycemic markers for prediabetic stage according to the American Diabetes Association [16].

Standard pulmonary function test
Spirometry was carried out with spirosift spirometer 5000 FUKDa NENSHI. Percent of predicted forced vital capacity (FVC, %pred), FEV1 %pred, FEV1 : FVC ratio (FEV1/FVC %), and forced expiratory flow rate 25–75 (FEF 25–75, %pred) were all measured, taking the best out of three technically satisfactory performances [17]. FEV1/FVC % is 70–80% in normal adults; values less than 70% reflect airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2].

Ethical considerations
Our study gained approval by the ethical committee board. All participants gave informed consent before enrollment. All participants were reassured about the confidentiality of the data, their right to withdraw from the study at any time without giving any reasons, and
without effecting their rights to medical care in case of refusal to participate.

**Statistical analyses**

Analysis of the collected data was done via the ‘Statistical Package for the Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) for Windows’ program, version 22.0. Mean±SD was calculated for continuous data, whereas number (percentage) was calculated for qualitative data. Analytical statistics was then performed between group I (ever smokers group) and group II (never smokers group) using the following: independent *t* test to compare between the two groups with normal continuous data distribution, Mann–Whitney test to compare between the two groups with nonnormal continuous data distribution, and *χ*² test or Fisher exact test to compare between two or many categorical groups. Finally, logistic regression analysis was done along with calculation of the odds ratios (ORs) and 95% confidence intervals (CI) to evaluate the probability of an FEV1/FVC, % <70% among different variables considered as potential risk predictors. *P* value less than 0.05 was considered statistically significant.

**Results**

Baseline characteristics of all 300 enrolled participants are summarized in Table 1. The two groups (ever versus never smokers) were matched for age, sex, and BMI with no statistically significant differences (*P*=0.2362 for age, *P*=0.3463 for sex, and *P*=0.209 for BMI).

Both indices of glycemic control were higher among participants of group I (ever smokers) compared with those of group II (never smokers), with a highly significant statistical difference between both groups

| Table 1 Baseline characteristics of the enrolled participants |
|-------------------------------------------------------------|
| **Age (years)**                                             |
| Range 40–62                                                 |
| Mean±SD 50.43±6.75                                         |
| **Sex [n (%)]**                                             |
| Male 137 (91.3)                                             |
| Female 13 (8.7)                                             |
| **BMI (kg/m²)**                                             |
| Range 21.5–36.1                                             |
| Mean±SD 27.75±4.27                                         |
| **SI (pack-years)**                                        |
| Range 18.0–38.1                                             |
| Mean±SD 27.83±6.70                                         |
| **Spirometry FVC, %pred**                                  |
| Range 65–95                                                 |
| Mean±SD 79.22±9.18                                         |
| **FEV1, %pred**                                             |
| Range 55–70                                                 |
| Mean±SD 62.63±4.44                                         |
| **FEV/FVC, %**                                              |
| Range 59.1–104.6                                            |
| Mean±SD 80.06±10.36                                        |
| <70% [n (%)]                                               |
| 26 (17.3)                                                  |
| **FEF25–75, %pred**                                        |
| Range 52–70                                                 |
| Mean±SD 60.77±5.86                                         |
| **Glycemic control indices FPG (mg/dl)**                    |
| Range 82–165                                                |
| Mean±SD 125.9±24.30                                        |
| **HbA1c (%)**                                               |
| Range 5.35–6.35                                             |
| Mean±SD 5.88±0.31                                          |

FEF 25–75, %pred, percent of predicted forced expiratory flow at 25–75% of the pulmonary volume; FEV1, %pred, percent of predicted forced expiratory volume in 1 s; FEV1/FVC, %, percent of ratio of FEV1 to FVC; FPG, fasting plasma glucose; FVC, %pred, percent of predicted forced vital capacity; HbA1c, glycated hemoglobin concentration; SI, smoking index. HS, highly significant, *P* value less than 0.01. NS, nonsignificant, *P* value more than or equal to 0.05. S, significant, *P* value less than 0.05.
On the contrary, spirometric parameters were lower in group I compared with group II, with a highly significant statistical difference regarding FVC, % pred ($P=0.0083$), FEV1, %pred ($P=0.001$), and FEF 25–75, %pred ($P=0.003$) and a significant statistical difference regarding FEV1/FVC, % ($P=0.042$).

Moreover, the prevalence of airflow obstruction as defined by FEV1/FVC, % less than 70% was higher among group I participants compared with group II [26/150 (17.3%) and 10/150 (6.7%), respectively] with a statistically significant difference between both groups ($P=0.042$).

In addition, Pearson correlation coefficient was calculated to investigate the association between the SI and each of the glycemic and spirometric indices in group I. Results revealed a significant positive correlation between SI and both FPG level ($r=0.462$, $P=0.015$) and HbA1c % ($r=0.377$, $P=0.021$) versus a significant inverse correlation with FVC, %pred ($r=-0.468$, $P=0.001$), FEV1, %pred ($r=-0.499$, $P=0.005$), FEV/FVC, % ($r=-0.426$, $P=0.002$), and FEF 25–75, %pred ($r=0.368$, $P=0.0311$) (Table 2).

Further analysis of the potential risk factors that might be associated with the occurrence of airflow obstruction (% FEV1/FVC<70%) among group I participants was then done. Comparing participating smokers with FEV1/FVC less than 70% with their counterparts with FEV1/FVC more than or equal to 70%, there was a statistical significant difference in age ($P=0.003$), BMI ($P=0.036$), SI ($P=0.016$), and both glycemic markers FPG ($P=0.016$) and HbA1c% ($P=0.041$), whereas there was no statistical difference regarding the sex of the enrolled participants ($P=0.218$) (Table 3).

Multivariable logistic regression was performed to evaluate the OR and 95% CI of airflow obstruction (FEV1/FVC, % <70%) associated with the aforementioned variables considered as potential risk predictors, including clinical variables age, BMI, cumulative smoking exposure quantified by SI, in addition to both of the glycemic control indices, FPG and HbA1c. Results of the current study revealed that the risk of developing FEV1/FVC, % less than 70% almost tripled among ever smokers with SI more than or equal to 25 pack-years (OR=3.11, 95% CI=1.85–3.66), with FPG more than or equal to 100 mg/dl (OR=2.91, 95% CI=1.62–4.01) and those who were more than or equal to 50 years (OR=2.85, 95% CI=1.69–3.99), whereas this risk doubled among ever smokers with BMI more than or equal to 25 kg/m² (OR=2.33, 95% CI=0.06–0.84) and HbA1c more than or equal to 5.6% (OR=2.07, 95% CI=0.12–0.77) (Table 4).

Discussion
Several epidemiological studies have gathered increasing body of evidence that tobacco smoke is an independent risk factor for COPD, insulin resistance, and type 2 DM [1,2], perhaps through initiation of systemic inflammation, which is common to both [8,9,18].

The presence of a common ground and a joint etiology between both diseases led us to hypothesize that an association between pulmonary function and glycemic status could possibly exist among cigarette smokers even at very early stages before clinical characteristics for either diseases became evident. If such hypothesis is valid and such an association could be established so that the existence of one could be a predictor for the other, this could be of great significance in the context of preventive medicine as early detection is key to disease control, delaying, and decreasing risk of complications as well as reducing medical costs.

In the current work, we aimed to clarify the association between pulmonary function tests, particularly airflow limitation, and two glycemic indices, namely, FPG and HbA1c, among asymptomatic apparently healthy cigarette smokers.

### Table 2 Correlation between smoking index and each of the glycemic and spirometric variables in group I (ever smokers’ group) (N=150)

| Smoking index (pack-years) | Pearson correlation r | P value |
|---------------------------|-----------------------|---------|
| HbA1c                     | 0.377                 | 0.021 S |
| FPG                       | 0.462                 | 0.015 S |
| %FVC                      | −0.468                | 0.001 HS|
| %FEV1                     | −0.499                | 0.005 HS|
| %FEV/FVC                  | −0.426                | 0.002 S |
| FEF 25–75                 | −0.368                | 0.0311 S|

FEV25–75, %pred, percent of predicted forced expiratory flow at 25–75% of the pulmonary volume; FEV1/FVC, %, percent of ratio of FEV1 to FVC; FPG, fasting plasma glucose; FVC, % pred, percent of predicted forced vital capacity; HbA1c, glycated hemoglobin concentration. HS, highly significant, P value less than 0.01. S, significant, P value less than 0.05.
FPG and HbA1c levels are recommended by the American Diabetes Association as diagnostic and screening tools for diabetes where elevated levels indicate IFG and chronic hyperglycemia, respectively [16]. IFG is a category of intermediate hyperglycemia but is not considered a clinical entity by itself, but it is a risk factor for future diabetes and diabetic complications. Moreover, it is associated with impaired secretion of insulin, whereas HbA1c concentration is a marker of long-term glucose homeostasis which reflects average plasma glucose in the past 2–3 months [19].

The main findings of the current work were that FEV1/FVC, % was significantly lower among ever smokers compared with never smokers, and the prevalence of FEV1/FVC less than 70% was higher among group I participants compared with group II (17.3 vs. 6.7%, respectively; \( P = 0.042 \)). Moreover, both FEV1, %pred and FEF 25–75, %pred values were significantly lower in group I versus group II (\( P = 0.001 \) for the former vs. \( P = 0.003 \) for the latter).

Both glycemic indices were significantly higher among ever smokers compared with never smokers (\( P = 0.001 \) for FPG level vs. \( P = 0.002 \) for HbA1c %), and the mean ±SD of both markers was also significantly higher among smokers with FEV1/FVC less than 70% than among their counterparts with FEV1/FVC more than or equal to 70% (124/150) (\( P = 0.016 \) for FPG vs. \( P = 0.041 \) for HbA1c %). These results are in accordance with those of Akpinar et al. [20] who reported that fasting hyperglycemia, one of the components of metabolic syndrome, was significantly prevalent among patients with COPD. Our results also match those of Baba et al. [3] who studied \( \sim 1000 \) apparently healthy Japanese volunteers and found that HbA1c levels were increased in patients having FEV1/FVC less than 70% than in patients without an airflow limitation. Moreover, Sato et al. [21] found a greater decline in FEV1 among smokers with metabolic

| Table 3 Comparison of potential risk factors associated with percent forced expiratory volume in 1 s/forced vital capacity ratio less than 70% in group I (ever smokers group) |
|---------------------------------|-----------------|-----------------|--------|
| Sex                             | %FEV/FVC (<70%) (N=26) | %FEV/FVC (≥70%) (N=124) | \( P \) value |
| Male/female                     | 20/6            | 117/7           | 0.218 NS |
| Age range                       | 40.0–62.0       | 40.0–60.0       | 0.003 HS |
| Age mean±SD                     | 52.96±7.30      | 48.90±6.54      |        |
| BMI range                       | 22.1–35.50      | 21.5–36.10      | 0.036 S |
| BMI mean±SD                     | 28.26±4.07      | 26.86±4.32      |        |
| SI range                        | 22.00–36.00     | 18.00–38.00     | 0.016 S |
| SI mean±SD                      | 29.69±5.24      | 26.10±5.82      |        |
| FPG range                       | 82.00–165.00    | 83.00–145.00    | 0.016 S |
| FPG mean±SD                     | 122.69±18.32    | 106.48±18.26    |        |
| HbA1c range                     | 5.35–6.35       | 5.35–6.35       | 0.041 S |
| HbA1c mean±SD                   | 5.94±0.34       | 5.81±0.31       |        |

Table 4 Multiple logistic regression analysis of different risk factors associated with percent forced expiratory volume in 1 s/forced vital capacity ratio less than 70%

| Factor                     | OR   | CI at 95.0% | \( P \) value |
|----------------------------|------|------------|-------------|
| Age (years)                |      |            |             |
| <50                        | 1.00 | 1.69–3.99  | 0.021 S     |
| ≥50                        | 2.85 |            |             |
| BMI (kg/m²)                |      |            |             |
| <25                        | 1.00 | 0.06–0.84  | 0.016 S     |
| ≥25                        | 2.33 |            |             |
| SI (pack-years)            |      |            |             |
| <25                        | 1.00 | 1.85–3.66  | 0.018 S     |
| ≥25                        | 3.11 |            |             |
| FPG (mg/dl)                |      |            |             |
| <100                       | 1.00 | 1.62–4.01  | 0.0068 HS   |
| ≥100                       | 2.91 |            |             |
| HbA1c (%)                  |      |            |             |
| <5.6                       | 1.00 | 0.12–0.77  | 0.026 S     |
| ≥5.6                       | 2.07 |            |             |

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin concentration; OR, odds ratio; SI, smoking index. HS, highly significant, \( P \) value less than 0.01. S, significant, \( P \) value less than 0.05. NS, nonsignificant, \( P \) value more than or equal to 0.05.

FPG and HbA1c levels are recommended by the American Diabetes Association as diagnostic and screening tools for diabetes where elevated levels indicate IFG and chronic hyperglycemia, respectively [16]. IFG is a category of intermediate hyperglycemia but is not considered a clinical entity by itself, but it is a risk factor for future diabetes and diabetic complications. Moreover, it is associated with impaired secretion of insulin, whereas HbA1c concentration is a marker of long-term glucose homeostasis which reflects average plasma glucose in the past 2–3 months [19].
syndrome and suggested that the underlying systemic inflammation may cause endothelial dysfunction, which might have a synergistic effect on the direct endothelial injury secondary to tobacco, resulting in enhanced annual decline in FEV1.

On studying the correlation between the total smoking exposure as quantified by the SI in pack-years and each of the aforementioned variables, results show significant inverse correlation between SI and % FEV/FVC ($r = -0.426, P = 0.002$), %FEV1 ($r = 0.499, P = 0.005$), and FEF 25–75 ($r = 0.368, P = 0.0311$) versus a significant positive correlation with both FPG level ($r = 0.462, P = 0.015$) and HbA1c % ($r = 0.377, P = 0.021$). These findings matched that of Sargeant et al. [8] who reported a dose–response relationship between HbA1c levels and daily number of cigarettes smoked and a positive association with SI. They added that the adjusted increase in HbA1c for a SI of 20 pack-years is 0.08 and 0.07% for men and women, respectively, concluding that cigarette smoking has long-term effect on glucose homeostasis.

Logistic regression analysis was conducted to determine the risk of developing airflow obstruction (FEV1/FVC < 70%) associated with different potential risk predictors, and our results showed that the risk was highest (three folds) with cumulative smoking exposure more than or equal to 25 pack-years (OR = 3.11, 95% CI = 1.85–5.66), with FPG more than or equal to 100 mg/dl (OR = 2.91, 95% CI = 1.62–4.01), and with age more than or equal to 50 years (OR = 2.85, 95% CI = 1.69–3.99), whereas the risk was less (two folds) with BMI more than or equal to 25 kg/m² (OR = 2.33, 95% CI = 0.6–0.84) and HbA1c more than or equal to 5.6% (OR = 2.07, 95% CI = 0.12–0.77).

Therefore, according to the results of this study, there was a higher likelihood of FEV1/FVC less than 70% with FPG levels of 100 mg/dl or above than with HbA1c% of 5.6% or more (OR = 2.91 vs. 2.07, respectively), which implies a stronger association between the occurrence of airflow limitation and the glucose tolerance status rather than glucose homeostasis. This finding is intriguing and rather difficult to explain because FPG reflects plasma glucose level at a certain point in time, whereas HbA1c gives estimated average plasma glucose levels for the past 2–3 months, which makes it a steadier and more reliable glycemic parameter. A possible explanation might be that elevated FPG and IFG might be transitory and reversible leading to bias in results as they are affected by several factors such as diet, stress [22], as well as the amount of cigarettes smoked at the time of testing because nicotine in tobacco smokers decreases insulin sensitivity by binding to nicotinic acetylcholine a1 receptors in human skeletal muscle, and this effect is proportional to the daily number of cigarettes smoked [23].

Some limitations of the present study should be mentioned: the study population had a small sample size, but we owe this to the relatively small number attending the health checkup clinic, as a relatively small percent of Egyptian population has the culture of doing regular checkups without having any complaints. Moreover, this was an observational study, in which the results reflect a certain point in time, so further longitudinal (follow-up) studies are needed to assess the progress of the findings. Moreover, the possibility of bias in selection cannot be denied, because we collected our data only from patients attending health checkup clinic, and further studies among different population groups are required to prove or disapprove our results. Moreover, we did not assay the oral glucose tolerance test, and therefore, underestimation of cases who have impaired glucose tolerance with fasting normoglycemia is a possibility. Furthermore, inflammatory markers reported to be related to lung dysfunction and the development of diabetes were not assessed. More studies are required to clarify the mechanisms linking risk of diabetes and lung dysfunction. These studies need to focus on data concerning insulin secretion and resistance, and other clinical markers related to diabetes and its development. Finally, our findings suggest association between airflow obstruction and impaired glycemic status, but association does not necessarily mean causation, and further studies are need to tackle this point.

**Conclusion**

Our results suggest an association and increased risk of COPD among asymptomatic cigarette smokers, current/former, especially elderly with impaired glucose homeostasis. Developing a risk score combining known risk factors for COPD including a measure of blood glucose in screening studies would be recommended.

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**Conflicts of interest**

There are no conflicts of interest.
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