The incidence of type 2 diabetes in patients with bronchial asthma

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Background
The effect of bronchial asthma on development of new-onset type 2 diabetes has not been studied.
Aim
The aim was to study the association of bronchial asthma and its severity with the incidence of type 2 diabetes after 5 years in patients without diabetes at the disease onset.
Patients and methods
A total of 200 consecutive patients with a physician diagnosis of bronchial asthma (120 not known to be diabetic and 80 known to have diabetes) presenting to the outpatient chest clinic in Kasr Alainy Hospital were included. Fasting blood glucose, 2 h 75 g oral glucose tolerance test, glycated hemoglobin, and lipid profile were done. Spirometry, blood pressure, BMI, and other risk factors of diabetes were sought.
Results
Of the 120 nondiabetic patients, 30 patients met at least one criterion of prediabetes and 90 patients met at least one criterion of diabetes. Multivariable regression model demonstrated that forced vital capacity (FVC)%, maximal expiratory flow 75%, and inhaled bronchodilators are independent risk factors for elevated glycated hemoglobin, independent of inhaled or oral corticosteroids, family history, blood pressure, BMI, high-density lipoprotein, and triglycerides. Logistic multivariable regression model demonstrated that FVC% and forced expiratory volume in the first second % are independent risk factors for development of new-onset type 2 diabetes (hazard ratio for FVC%: 1.1589, 95% confidence interval: 1.0684–1.2571, P=0.0004; hazard ratio for forced expiratory volume in the first second %: 0.8754, 95% confidence interval: 0.8155–0.9396, P=0.0002).
Conclusion
The incidence of diabetes and prediabetes in patients with bronchial asthma who are not known to have diabetes at disease onset is 75 and 25%, respectively. Poor pulmonary function tests were independently associated with new-onset diabetes in such patients. This association is linked to the severity of asthma and not related to treatment.

Keywords:
bronchial asthma, incidence, pulmonary function tests, type 2 diabetes mellitus

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Introduction

Correlations between bronchial asthma and type 2 diabetes have been sought in previous literature studies [1,2]. Results have been overall controversial, though significant in female patients [3]. Bronchial asthma as a consequence of diabetes is well established through specific pathways. First, chronic inflammation associated with diabetes was incriminated in reducing lung functions. Later, high glucose concentration was found to result in bronchial hyperresponsiveness via a Rho/Rho-associated kinase (ROCK) and myosin phosphatase targeting subunit 1 (pMYPT1)-dependent pathway *in vitro* [4]. Moreover, this effect was found to be blocked by GLP-1 receptor stimulation, which also modulates glucose metabolism [5]. On the contrary, the effect of bronchial asthma on development of new-onset type 2 diabetes is less studied. This effect was mainly attributed to the use of corticosteroids, inducing or unmasking insulin resistance [2]. Moreover, chronic inflammation associated with bronchial asthma can lead to the metabolic syndrome and insulin resistance [6,7]. This chronic inflammatory process is demonstrated by elevation of serum inflammatory marker levels and appears to function in both directions as mentioned earlier [8]. This work aims to study the association of bronchial asthma and its severity with the

incidence of type 2 diabetes after 5 years in patients without diabetes at the disease onset and to seek the effect of bronchial asthma and its severity on diabetes control in patients already on oral hypoglycemic.

Patients and methods

Population of study and disease condition

The study comprises 200 consecutive patients with a physician diagnosis of bronchial asthma, presenting to the outpatient chest clinic in Kasr Alainy Hospital for follow-up. The patient cohort was enrolled in 2018. Patients with disease duration less than 5 years were excluded. The study comprised 80 patients with known type 2 diabetes on oral therapy and 120 patients with a negative history of diabetes mellitus. Patients with other obstructive lung diseases were excluded. Diabetic patients on insulin were excluded.

The research protocol was approved by the Medical Ethics Committee of Kasr Alainy Medical School, Cairo University. A written informed consent was obtained from all participants. In case patients were unable to provide consent, it was taken from designated surrogates.

Laboratory workup was done for all patients, including fasting blood glucose, 2 h 75 g oral glucose tolerance test, glycated hemoglobin (HBa1c), lipid profile, and complete blood picture. Detailed drug history for treatment of bronchial asthma and diabetes where appropriate was sought. History regarding conventional risk factors for type 2 diabetes was recorded including positive family history, gestational diabetes, or delivery of a large baby in female patients.

Clinical examination was done for all patients. Blood pressure was measured, and BMI was calculated in kg/m^2. Spirometry was done to all patients.

Statistical analysis

Data were analyzed using the MedCalc Statistical Software version 19.0.3 (MedCalc Software bvba, Ostend, Belgium). Parametric data were presented as mean±SEM, whereas nonparametric data were presented as median and percentiles for quantitative variables, whereas frequency and percentages were used for qualitative variables. Differences were calculated by χ^2 and Fisher's exact tests (for categorical variables) or the Student *t*-test. Pearson's correlation coefficient was used with 95% confidence intervals. *P* value less than 0.05 was considered significant. Backward multivariable regression model was done to identify independent risk factors for continuous variables, that is, increased different blood glucose markers. Logistic multivariable regression model (backward) was done to identify independent risk factors for categorical variables, that is, occurrence of new-onset diabetes.

Results

Table 1 shows the mean and standard error of various variables among different groups of patients according to presence of diabetes.

Glucose testing including fasting blood sugar, 2 h postprandial, and glycated hemoglobin in the 120 patients without any prior history of diabetes

Fasting blood sugar (FBS) was normal (<100 mg/dl) in 27 (22.5%) patients, impaired (≥100 and <126 mg/dl) in 60 (50%) patients, and elevated (≥126 mg/dl) in 33 (27.5%) patients (Figure 1).

Postprandial glucose was normal (<140 mg/dl) in nine (7.5%) patients, impaired (≥140 and <200 mg/dl) in 96 (80%) patients, and elevated (≥200 mg/dl) in 15 (12.5%) patients (Figure 2).

HBa1c was normal (≤5.6%) in none of the patients (0%), impaired (>5.6%) in 33 (27.5%) patients, and elevated (≥6.5%) in 87 (72.5%) patients (Figure 3).

To sum up the previous results, we found out the following:

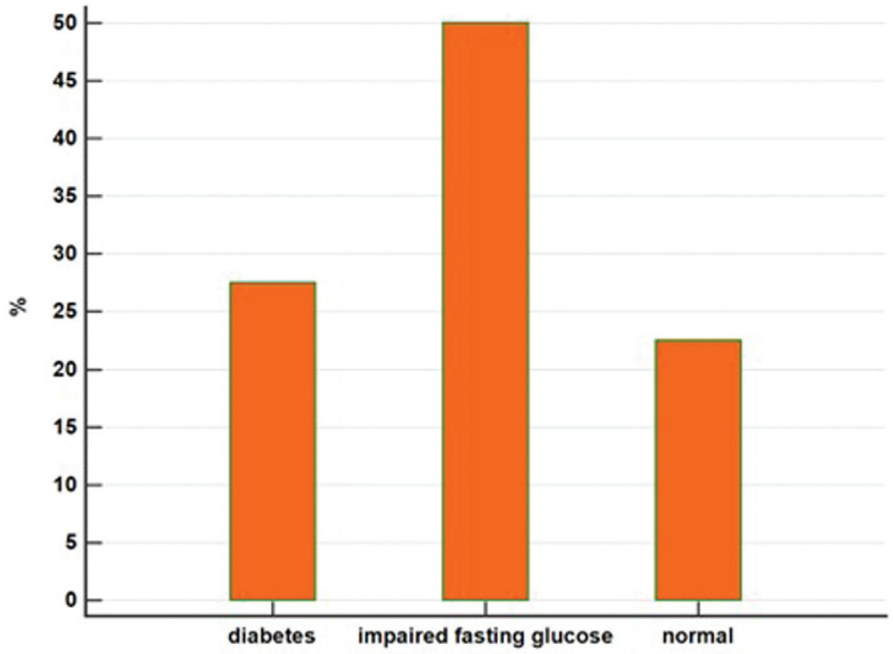
A total of 30 (25%) patients met at least one criterion of prediabetes: impaired fasting glucose (≥100 and

Table 1 Mean and SE of various variables among different groups of patients according to presence of diabetes

	Prediabetes (*n*=30)		New-onset diabetes (*n*=90)		Diabetes on oral therapy (*n*=80)	
	Mean	SEM	Mean	SEM	Mean	SEM
FBS	111.100	2.6658	120.800	2.9578	201.200	15.3752
2 h PP	165.000	3.9427	171.933	2.4300	277.312	12.0995
HbA1c	6.090	0.04351	6.803	0.02314	8.639	0.1589
FVC%	85.500	1.8066	87.100	1.3576	79.413	2.2559
FEV1%	94.100	2.9460	89.367	1.4494	76.200	2.8272
FEV1_FVC%	91.800	1.0366	87.300	0.7496	79.606	1.9061
MEF75%	99.400	5.1663	84.767	2.1337	69.325	4.1692

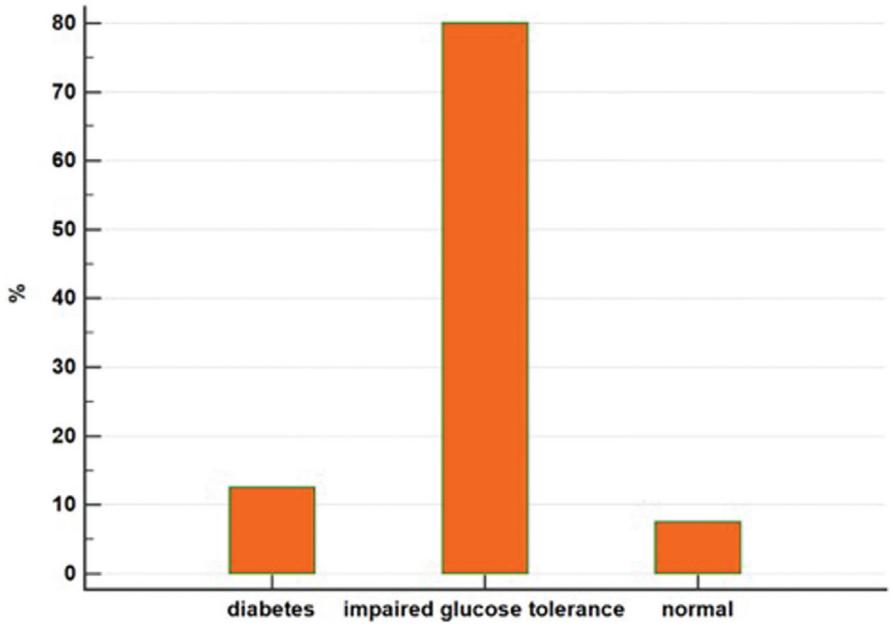
2 h pp, 2 h postprandial blood sugar; FBS, fasting blood sugar; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HbA1c, glycated hemoglobin; MEF75, maximal expiratory flow.

Figure 1



Frequency of patients without prior history of diabetes (n=120) according to fasting blood glucose.

Figure 2



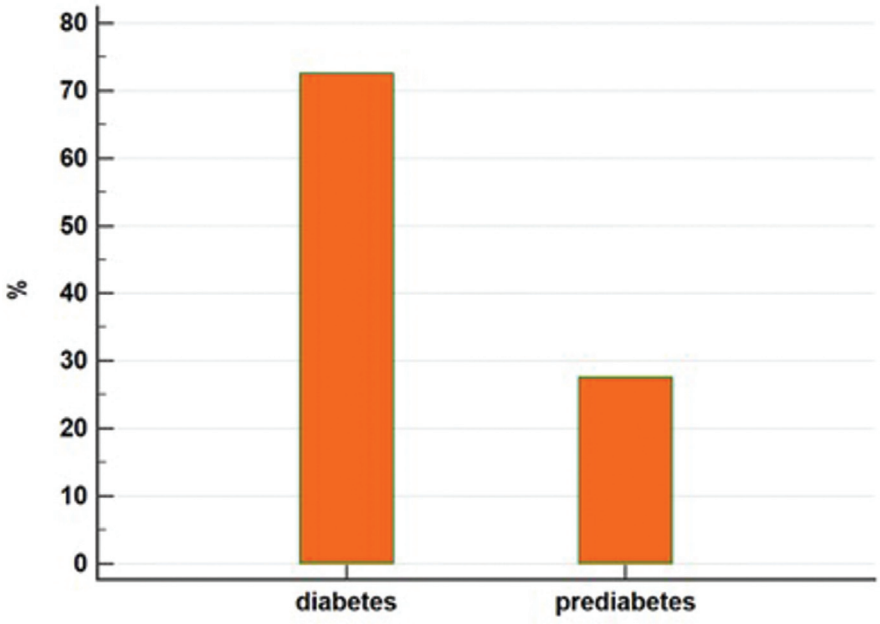
Frequency of patients without prior history of diabetes (n=120) according to 2 h oral glucose tolerance test.

<126 mg/dl), impaired glucose tolerance (≥140 and <200 mg/dl), and/or HBa1c greater than 5.6.

The remaining 90 (75%) patients met at least one criterion of diabetes: fasting glucose (≥126 mg/dl), impaired glucose tolerance (≥200 mg/dl), and/or HBa1c up to 6.5.

Multivariable regression analysis was done in the 120 patients without any prior history of diabetes, to test for various variables as independent risk factors for elevation of FBS, postprandial blood glucose, and HBa1c. The model included pulmonary function test parameters, drug history (inhaled bronchodilators, inhaled or oral corticosteroids), as

Figure 3



Frequency of patients without prior history of diabetes (*n*=120) according to glycated hemoglobin.

well as classic risk factors of diabetes such as family history, blood pressure, BMI, high-density lipoprotein, and triglycerides. The model was repeated for each of FBS, postprandial blood glucose, and HBa1c:

Multivariable regression model also demonstrated that forced vital capacity (FVC)%, forced expiratory volume in the first second (FEV1)/FVC%, maximal expiratory flow (MEF)75%, inhaled bronchodilators, and oral corticosteroids are independent risk factors for elevated FBS in patients not known to have diabetes. Table 2 shows the *P* values and partial correlation coefficients (after adjusting the effect of other variables) of significant independent risk factors for FBS elevation in patients not known to have diabetes.

As for postprandial blood glucose, multivariable regression model demonstrated that FEV1/FVC%, MEF75%, inhaled corticosteroids, and oral corticosteroids are independent risk factors for elevated postprandial blood glucose in patients not known to have diabetes. Table 3 shows the *P* values and partial correlation coefficients (after adjusting the effect of other variables) of significant independent risk factors for postprandial blood glucose elevation in patients not known to have diabetes.

Moreover, multivariable regression model demonstrated that FVC%, MEF75%, and inhaled bronchodilators are independent risk factors for elevated HBa1c in patients not known to have diabetes. Table 4 shows the *P* values and partial correlation coefficients (after adjusting the effect of other variables) of significant independent risk factors for HBa1c elevation in patients not known to have diabetes.

Table 2 *P* values and partial correlation coefficients (after adjusting the effect of other variables) of significant independent risk factors for fasting blood sugar elevation in patients not known to have diabetes (*n*=120)

Independent variables	Partial correlation coefficient *r*	*P*
FVC%	0.4767	<0.0001
FEV1_FVC%	0.1915	0.0113
MEF75%	0.2991	0.0001
IBD	0.3081	0.0001
OCS	0.2731	0.0004

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; IBD, inhaled bronchodilator; MEF75, maximal expiratory flow; OCS, oral corticosteroids.

Table 3 *P* values and partial correlation coefficients (after adjusting the effect of other variables) of significant independent risk factors for postprandial glucose elevation in patients not known to have diabetes (*n*=120)

Independent variables	Partial correlation coefficient *r*	*P*
FEV1_FVC%	0.2640	0.0004
MEF75%	0.1986	0.0071
ICS	0.2967	0.0001
OCS	0.5070	<0.0001

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; IBD, inhaled bronchodilator; MEF75, maximal expiratory flow; OCS, oral corticosteroids.

Logistic multivariable regression analysis was done in the 120 patients without any prior history of diabetes,

Table 4 *P* values and partial correlation coefficients (after adjusting the effect of other variables) of significant independent risk factors for glycated hemoglobin elevation in patients not known to have diabetes

Independent variables	Partial correlation coefficient *r*	*P*
FVC%	0.2029	0.0183
MEF75%	0.3136	0.0003
IBD	0.2405	0.0054

FVC, forced vital capacity; IBD, inhaled bronchodilator; MEF75, maximal expiratory flow

Table 5 Odds ratios with 95% confidence intervals and *P* values of significant independent risk factors for development of new-onset type 2 diabetes in patients not known to have diabetes

Independent variables	Odds ratio	95% CI	*P*
FVC%	1.1589	1.0684 to 1.2571	0.0004
FEV1%	0.8754	0.8155 to 0.9396	0.0002

CI, confidence interval; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity

to test for various variables as independent risk factors for development of new-onset type 2 diabetes. The model included pulmonary function test parameters, drug history (inhaled bronchodilators and inhaled or oral corticosteroids) as well as classic risk factors of diabetes such as family history, blood pressure, BMI, high-density lipoprotein, and triglycerides.

FVC% and FEV% were found to be independent risk factors for development of new-onset type 2 diabetes in patients not known to have diabetes. Table 5 shows odds ratios with 95% confidence intervals and *P* values of significant independent risk factors for development of new-onset type 2 diabetes in patients not known to have diabetes.

Multivariable regression analysis was done in the 80 patients known to have diabetes on oral hypoglycemics, to test for various variables as independent risk factors for poor control of diabetes. The model included pulmonary function test parameters and drug history (inhaled bronchodilators and inhaled or oral corticosteroids). The model was repeated for each of FBS, postprandial blood glucose, and HBa1c.

Only oral corticosteroid therapy was found to be a significant independent risk factor for higher levels of FBS, postprandial blood glucose, as well as HBa1c. Pulmonary function test parameters showed no significance. Table 6 shows the *P* values and partial correlation coefficients (after adjusting the effect of other variables) of oral corticosteroid medication as a significant independent risk factor for FBS, postprandial blood glucose, and HBa1c elevation in patients with diabetes mellitus on oral hypoglycemic drugs.

Table 6 *P* values and partial correlation coefficients (after adjusting the effect of other variables) of oral corticosteroid medication as a significant independent risk factor for fasting blood sugar, postprandial blood glucose, and glycated hemoglobin elevation respectively, in patients with diabetes mellitus on oral hypoglycemic drugs.

Dependent variables	Partial correlation coefficient *r*	*P*
FBS	0.2461	0.0278
Postprandial glucose	0.3993	0.0002
HBa1c	0.3204	0.0038

FBS, fasting blood sugar; HBa1c, glycated hemoglobin.

Discussion

Patients with bronchial asthma and poor pulmonary functions are likely to receive higher corticosteroid doses with an increased risk of developing diabetes. However, the study demonstrates pulmonary function deterioration as independent risk factors for elevation of blood glucose levels in patients who are not known to have diabetes. This was in addition to oral corticosteroids in the case of FBS and inhaled corticosteroids in the case of postprandial blood glucose.

Interestingly, pulmonary functions showed no significant effect on blood glucose levels in patients with diabetes. Poor glycemic control was attributed only to corticosteroid intake.

This contrast between the two cohort groups supports an independent pathophysiological role related to the chronic inflammatory process in bronchial asthma in causing necessary metabolic derangements for the development of new-onset diabetes.

Poor pulmonary function tests were independently associated with new-onset diabetes in patients with bronchial asthma taking into account various risk factors including oral and inhaled corticosteroids. Therefore, it is clear that a direct association should be sought for development of new-onset diabetes that is linked to the severity of asthma and not related to treatment [9]. Bronchial asthma is known to be associated with increased expression of interleukin (IL)-4. IL-4 increases immunoglobulin E secretion and has a key role in bronchial asthma pathology. This role can be reversed by blocking IL-4 with soluble receptors with subsequent improvement of pulmonary functions [10]. This cytokine has also been recently implicated in diabetes, obesity, and insulin resistance [11].IL-4 thus is an important

example for common pathways triggering new-onset diabetes in patients with asthma.

The incidence of diabetes and prediabetes in the study cohort was enormous, rendering none of the patients totally free of metabolic affection. The authors recommend routine screening for diabetes and prediabetes in such patients, considering glucose intolerance as an important complication of bronchial asthma that affects its prognosis.

The incidence rates of IBD, RA, DM, and CAD in non-asthma were 16.7, 55.3, 104, and 134 per 100,000, respectively whereas those for asthmatics were 21.2, 81.8, 138.4, and 188.6 per 100,000, respectively [12].

In conclusion, early detection of co-morbid conditions such as T2D in patients with bronchial asthma is mandatory to enable us to individualize the management plans accordingly. Systemic evaluation as well as pulmonary functions tests should be stressed upon during patients follow up visits whether diabetes is present or not. This aims at minimizing the long-term complications of both asthma and T2D which would happen if any of them was left untreated.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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