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The Prevalence of Diabetes Mellitus Type 2 in Severe and Very Severe Chronic Obstructive Pulmonary Disease Patients

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide. There is evidence to support a connection between COPD and Diabetes mellitus type 2 (T2DM). T2DM affects 2-37% of COPD patients, with results being highly variable between studies.

Objective To determine the prevalence of T2DM in patients with severe and very severe stages of COPD and to assess the risk factors affecting the prevalence of T2DM among COPD patients.

Methods A cross sectional study was conducted on 140 patients with COPD attending Outpatient and Inpatient of Respiratory Unit at Baghdad Teaching Hospital. The data were collected between the 10th of October 2016 to the 10th of August 2017. These data included demographic parameters such as: age, sex, smoking habit, and respiratory parameters from history and clinical examination. Spirometry was used to assess the severity of COPD patients. Random blood sugar testing was used for identification of COPD patients having T2DM when they are not clear or not known as a case of T2DM previously.

Results The prevalence of T2DM among COPD patients was 19.38%; the prevalence of T2DM in those with severe stage was 10.9%, while in very severe stage was 35.4%. In comparison to women, men were more likely to have T2DM.The prevalence of T2DM increased in the elderly COPD patients (>61 years), with high body mass index, and also increased more among current smokers followed by former smokers and never smokers. Lung function tests decline more in COPD patients with presence of T2DM.

Conclusion T2DM is more common among COPD patients, and its prevalence rose as the severity of the COPD patients' condition worsened. Additionally, T2DM patients are more likely to experience a decline in pulmonary function.

Keywords Diabetes mellitus type 2, chronic obstructive pulmonary disease, prevalence, random blood sugar

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List of abbreviations: COPD = Chronic obstructive pulmonary disease, FEV1 = Expiratory volume in first second, FVC = Forced vital capacity, T2DM = Type 2 Diabetes mellitus

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable condition, characterized by airflow limitation that is usually progressive and associated with chronic inflammatory response in airways due to harmful, noxious particles or gases, especially in tobacco smoking exposure. Exacerbations and associated comorbidities with a significant extra pulmonary problem which may contribute to the severity in different patients [(1)].

Between 1.6 and 16% of COPD patients have diabetes, according to reports. Smoking has

been identified as a risk factor for diabetes, similar to COPD, and the risk is reduced by quitting for more than 5 to 10 years. Type 2 diabetes (T2DM) is more prevalent in moderate-to-very severe (but not mild) COPD than in the general population [2]. The evidence for an interaction between T2DM and COPD is supported by studies that demonstrate reduced lung function as a risk factor for the development of diabetes. Inflammatory mediators such as Tumor necrosis factor alpha (TNF-α), Interleukin-6 (IL-6), and C-reactive protein (CRP), which are elevated in COPD, are also increased in diabetes. The impact of parental use of corticosteroids on the management of diabetes during COPD exacerbations and the effect of diabetes control on COPD outcomes are of great clinical concern [3]. According to World Health Organization (WHO) report in 2020, 212.3 million prevalent cases of COPD were reported globally, with COPD accounting for 3.3 million deaths and 74.4 million Disability adjusted life per years (DALYs) [4].

The intersection of T2DM and CPOD may be one of the important epidemiological bridges [3]. Numerous researches have shown that diabetics have significantly lower lung function, and more recent studies have revealed that DM is a common concomitant illness in COPD patients. The strong association between T2DM and COPD is due to multiple interrelated factors and through different mechanisms, including shared risk factors, direct causation in addition to treatment effect. Cigarette smoking is known to be the primary cause of COPD. Additionally, smoking increases insulin resistance, and individuals who smoke have a 30–40% higher risk of developing type 2 diabetes than those who don't [5].

T2DM and COPD share a similar insidious onset, which usually leads to late presentation and diagnosis. Recognition of T2DM and/or COPD may be even more difficult in patients who already diagnosed with the other pathologies, particularly where they are consulted an organ-based specialist [6]. Patients with diabetes who experience chronic pulmonary damage (progressive and irreversible damage) due to diminished lung function and volumes, several functional abnormalities in the respiratory tract, pulmonary autonomic neuropathy, and decreased pulmonary diffusing capacity for carbon monoxide would simply exercise less, occasionally complain of dyspnea with exertion, and have annoyance-inducing seasonal upper respiratory symptoms. All of these symptoms might be inferred by specialist or family doctor to start treatment of COPD, diabetes and lifestyle modification accordingly [7,8].

The study objectives were to determine the prevalence of T2DM in severe and very severe stages of COPD patients. Additionally, to assess the risk factors affecting the prevalence of T2DM among COPD patients.

Methods

A cross sectional study was conducted on 140 patients with COPD attending Outpatient and Inpatient of Respiratory Unit at Baghdad Teaching Hospital. A random sample were collected between the 10th of October 2016 to the 10th of August 2017. The data included demographic parameters; age, sex, occupation, smoking habit, and respiratory parameters from history and clinical examination, chest radiography and medications used by the patient currently or previously, symptoms related to respiratory system, duration of illness, level of dyspnea {Medical Research Council range (0-4)}, number of exacerbations. Concerning information about T2DM, history of T2DM, duration of T2DM, taking antidiabetic agents, family history of DM was also reported. The inclusion criteria were post bronchodilator spirometry obstruction defined as expiratory volume in first second (FEV1)/ forced vital capacity (FVC) ratio <0.70. Patients aged more than 40 years, and diagnosed with COPD and classified according to criteria of Global Initiative for COPD into severe and very severe stage [9].

The exclusion criteria included patients with any other lung disease other than COPD, patients on systemic steroid therapy, T1DM patients, patients with incomplete questionnaires, no medical and demographic information, no spirometry, no laboratory tests) or FEV1/FVC ratio >0.70 after administration of bronchodilator. Informed consent was obtained from all the participants for the investigations needed and the purpose of the study.

Diagnosis of COPD

All the participants enrolled in this study were subjected to spirometry testing. Several measures of lung function were FEV1, FVC, and post bronchodilator FEV1/FVC ratio.

They were measured by office spirometry in pulmonary function test in Outpatient Clinic at Baghdad Teaching Hospital. Using modification of the criteria developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [9], the subjects were classified according to their GOLD COPD stage as follows:

- Stage 1 (mild): FEV1 ≥80% of predicted; FEV1/FVC <0.70.
- Stage 2 (moderate): FEV1 ≥50 to <80% of predicted and FEV1/FVC <0.70.
- Stage 3 (severe): FEV1 ≥30 to <50% of predicted and FEV1/FVC <0.70.
- Stage 4 (very severe): FEV1 <30% of predicted and FEV1/FVC <0.70.

Diagnosis of T2DM

The diagnosis of T2DM was according to American Diabetes Association (ADA), subjects already known to have T2DM were directly enrolled in this study as known cases with COPD patients. The subjects whose diabetes status was unclear underwent random blood sugar (RBS) testing, and if more than 200 mg/dl (11.1 mmol/L) with classic symptoms of hyperglycemia. They were classified as new T2DM cases with COPD. Late onset T1DM (LADA) was ruled out in this cohort in newly diagnosed patient by follow those patients specifically for the definite diagnosis [10].

Smoking status

The subjects enrolled in this study were classified according to smoking status into:

- Never smoker: They never smoked or who smoked fewer than 100 cigarettes in their entire lifetime.
- Current smoker: They had smoked at least 100 cigarettes in their entire life and still smoking.
- Former smokers: They smoked at least 100 cigarettes in their life but not currently smoking.

The calculated number of pack-years = years of smoking X number of daily smoked cigarettes/ 20 [11].

Statistical analysis

Statistical analysis was performed with the Soft Package Scientific Statistics, version 22.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD) and 95% confidence interval (95% CI) and categorical variables were presented as percentages. Chie-square test was used to determine the associations between the categorical variables. P-value is equal or less than 0.05 was considered as the level of significance was).

Results

Sample characteristics

A total of 140 patients diagnosed as COPD were selected in this study. There were 92 (65.7%) COPD patients with severe and 48 (34.3%) with very severe stage. Their age ranged from 42 to 84 years with a mean±SD of 58.6±8.4 years. Females were 43 (30.7%) and 97 (69.3%) were males, giving a male to female ratio of 2.25:1. There were 62 (44.3%) current smokers, 55 (39.3%) former smokers and 23 (16.4%) never smokers. COPD patients with severe and very severe stage were insignificant different age groups (p>0.05), the rates of patients diagnosed COPD with severe and very severe stage consisted from males (70.1% and 29.9%, respectively). The proportion of COPD patients with severe and very severe stage was

found to be higher in current smokers (41.3% and 50%, respectively). A positive correlation between prolong duration of COPD and increasing severity of COPD with-risk of T2DM (Table 1).

Table 1. Demographic characteristics of the study group

Variable	Categories	All COPD N=140 No. (%)	Severe COPD N=92 (65.7%) No. (%)	Very Severe COPD N=48 (34.3%) No. (%)	P value
Age group (yr)	41-50	31 (22.1)	21 (22.8)	10 (20.8)	0.952
	51-60	29 (20.7)	20 (21.7)	9 (18.8)	
	61-70	38 (27.2)	24 (26.1)	14 (29.2)	
	>70	42 (30.0)	27 (29.4)	15 (31.2)	
Sex	Male	97 (69.3)	68 (73.9)	29 (60.4)	0.021
	Female	43 (30.7)	24 (26.1)	19 (39.6)	
Smoking status	Current	62 (44.3)	38 (41.1)	24 (50.0)	0.018
	Former	55 (39.3)	33 (35.7)	22 (45.8)	
	Never	23 (16.4)	21 (22.8)	2 (4.2)	
			Mean±SD	**Mean±SD**	
Respiratory function test	FVC L		1.63±0.3	1.1±0.6	<0.001
	FVC% Pred.		53.4±10.6	36.8±11.2	<0.001
	FEV1 L		1.1±0.8	0.69±0.3	<0.001
	FEV1% Pred.		41.7±3.1	25.7±5.4	<0.001
	FEV1/FVC%		62.1±3.7	49.2±7.4	<0.013
Duration of COPD (yr)			8.4±4.3	11.7±8.2	0.011
RBS (mmol/l)			9.6±0.5	12.3±1.5	<0.001

COPD: Chronic obstructive pulmonary disease, FEV1: Forced expiratory volume at first second, FVC: Forced vital capacity, RBS: Random blood sugar

Prevalence

The overall prevalence of T2DM detected among COPD patients with severe and very severe stage was found to be 19.28% (27/140). A higher prevalence of T2DM was detected among COPD patients with very severe stage (35.4%) (17/48) when compared to that in COPD patients with severe stage (10.9%) (10/92). A statistically significant difference (P<0.05) was found to exist in this case. This table also showed insignificantly higher prevalence of T2DM among male COPD patients in both severe (7.6%) and very severe stage (25%) than in females (3.3% and 10.4%, respectively) (p>0.05). The prevalence of DM was significantly higher among COPD patients with very sever stage at age group more than 60 years (>60 years) when compared to those below 60 years old (<60 years) (p<0.05) (Table 2).

Table (3) showed the differences in the mean values of pulmonary function tests between the COPD patients with T2DM and without T2DM. It showed a statistical difference between COPD patient with T2DM and without T2DM regarding the pulmonary function tests including FVC L, FEV1 L, FEV1/FVC%, FEV% Predicted, and FVC% Predicted (P<0.05).

Table 2. Prevalence of Type 2 diabetes mellitus among the study groups according to gender, age and smoking

Variable		Severe COPD with T2DM N=10 No. (%)	Very Severe COPD with T2DM N=17 No. (%)	P value
Gender	Males	7 (7.6)	12 (25.0)	0.974
	Females	3 (3.3)	5 (10.4)	
Age group (yr)	40-60	1 (1.1)	8 (16.65)	0.049
	61-70	4 (4.3)	4 (8.3)	
	>70	5 (5.4)	5 (14.4)	
Smoking	Never	1 (1.1)	3 (6.3)	0.862
	Former smokers	4 (4.3)	6 (12.5)	
	Current smoker	5 (5.4)	8 (16.7)	

COPD: Chronic obstructive pulmonary disease, T2DM: Type 2 diabetes mellitus

Table 3. Mean pulmonary function test values among chronic obstructive pulmonary disease patients with or without presence of type 2 diabetes mellitus

Pulmonary function test	COPD with T2DM N=27 Mean±SD	COPD without T2DM N=113 Mean±SD	P-value
FVC L	0.9±0.2	1.4±0.4	<0.0001
FEV1 L	0.7±0.3	1.2±0.6	0.001
FEV1/FVC%	48.3±6.2	63.2± 2.9	<0.0001
FEV1% pred.	23.8±5.3	40.9±2.8	<0.001
FVC% Pred.	35.2±7.3	54.1±9.4	<0.0001

COPD: Chronic obstructive pulmonary disease, T2DM: Type 2 diabetes mellitus, FEV1: Forced expiratory volume at first second, FVC: Forced vital capacity

Discussion

Many previous studies had agreed in predicting an increase in COPD morbidity and mortality. At 2020, COPD is expected to cause over 6 million deaths annually around the world, as a result, it rose to the third-ranking cause of death worldwide [12]. Through understanding the pathophysiology of COPD, and the concept of systemic inflammation, they had been helped to explain the high frequency of major and important co morbidities such as T2DM. In addition to coexisting conditions that one would naturally expect due to the patients' advanced age and due to other associated risk factors, such as smoking, stress, sedentary life style, physical activity, unhealthy diet habit, etc. [13,14].

The present study revealed that the overall prevalence of T2DM among COPD patients with severe and very severe stage was 19.3% (10.9 % in severe stage and 35.4% in very severe stage). It is significantly higher if compared to the overall prevalence of diabetes in the general Iraqi population for adults aged 20-79 years of 9.4% [15].

The prevalence of T2DM in current study is in line with various studies reported from different countries. In a cohort study conducted in Taiwan by Ho et al., 2017, whom found that during a period of 10 years follow

up, 304 (19%) of 1568 COPD patients developed incident DM [16]. This result was also similar to a survey conducted by Stojkovikj et al. 2016, who found that 21% of Macedonian COPD patients with severe and very severe stage reported T2DM [17]. However, current results were lower than that reported by Mahishale et al. study 2015, who found 25.63% of Indian patients with COPD having T2DM and concluded that very severe COPD was associated with a higher risk of T2DM [18].

The possible development of COPD and T2DM, could have evidence in the context of a chronic systemic inflammation with the presence of cardiovascular or other metabolic disorders, known to cause systemic inflammation, increasing the association between COPD and T2DM [19]. There are multiple factors such as inflammation or disease-related inflammation, oxidative stress, hypoxia, reduced physical activity, and smoking habit in addition to hyperglycemia, which may contribute to the higher prevalence of diabetes in COPD. It found that the treatment with corticosteroids is considered to be another factor that may increase the risk of the association between these two diseases [20].

In terms of age, this study revealed that T2DM was more common in COPD patients with severe and very severe stages at 60 years. Moreover, it was higher among COPD patients with very severe when compared to that of severe stage. This is in agreement with many studies reported elsewhere by Shen et al. (2014) in Taiwan, who found a higher risk of developing lung cancer and T2DM among COPD patients at age group more than 60 in comparison with COPD patients at age below than 60 years old [21]. In a cross-sectional analytic study, Feary et al. (2010) revealed that there is a decrease in diabetes in older COPD patients; if diabetes is connected with COPD, the biggest effects are seen in the youngest COPD patients who smoke and those between the ages of 45 and 55 who have never smoked. [22]. This could be due to the fact that elderly people are more exposed to risk factors in COPD patients as comorbidities such as hypertension, heart failure, osteoporosis, metabolic disorders, pulmonary hypertension, which may enhance for increasing risk of T2DM in those subjects [23]. Moreover, elderly people are more exposed to frequent infections, systemic inflammations, frequent hospitalizations, high symptoms score, history of frequent and changing in current and previous medications, limited physical activity, poor in their lifestyle, all these factors may play role as the root of many chronic diseases including COPD and T2DM [24].

In a study of 100 people with COPD, Stojkovki et al. (2016) discovered that male patients with severe and very severe COPD had an insignificantly greater prevalence of T2DM than female patients [25]. The differences in the prevalence of T2DM among COPD patients with severe and very severe may be related to the fact that male-female differences are divided into sex-related differences as in (biological variability) and (environmental and socio-cultural factors such as occupational exposure, smoking exposure as active and passive that may have effect on the pulmonary impairment, since the vast majority of our patients were smokers, although some one reported that the development of COPD more prevalent among females because a large percentage of them were smokers and their life style was changed mainly in developed countries [26,27].

Concerning smoking status; this study showed that the prevalence of T2DM in severe and very severe of COPD patients was higher among current smokers (5.4% and 16.7%, respectively) followed in order by former smokers (4.3% and 12.4%), and never smokers (1.1% and 6.3%). This finding suggested that smoking factor may play a role in the increasing the risk for development of T2DM among COPD patients in both the severe and very severe stage. Similarly, many studies have found that T2DM was more prevalent among COPD patients. In subjects who smoke, the adverse effects of T2DM on lung function were even greater. It found that cigarette smokers were 30% to 40% more likely to develop T2DM than non-smokers

and because cigarette smoking increases insulin resistance [14]. Tobacco exposure is common risk factor for both COPD and the co-morbidities including T2DM. The present study as well as many other studies emphasize the urgent need for smoking cessation programs at all levels of healthcare services. It is essential to note that interventions to decrease the prevalence of smoking among patients with COPD (or in the general population) may have an important impact on the prevalence of COPD and comorbidities such as T2DM.

Regarding pulmonary function; the present study revealed that there is a significant declining or impairment in the pulmonary function among COPD patients with T2DM in severe and very stage in comparison with COPD patients without T2DM. This finding was in agreement with many studies carried out in different countries that found a correlation between lung volumes and development of T2DM [12]. It should be noted that some studies found no association between lung function and the presence of T2DM [28-30]. A study conducted by Mekov et al. (2015) found no differences in FVC, FEV1 according to presence of T2DM among COPD patients while there was a significant difference in FEV1/FVC ratio [31]. Subjects with diabetes are at increased risk of several pulmonary conditions including COPD [32]. The direct association between impaired lung function and diabetes is thought to be the result of biochemical changes in the structures of the lung tissue and airways that involve a series of mechanisms likely due to reduced physical activity, smoking habit, systemic inflammation, oxidative stress, and hypoxemia, all may contribute to the higher prevalence of T2DM in COPD patients [33].

The limitations of this study were the small sample size recruited in this study affect the significant differences among COPD specially regarding the association between the prevalence of T2DM and other potential variables. In addition to the diagnosis depended only on RBS of the COPD, which affect the real prevalence of diabetes especially the newly established T2DM among COPD patients.

In conclusion; T2DM was more prevalent in male COPD patients with severe and very severe but there is no significant difference especially current smokers and older age group. In COPD patients with T2DM, declining lung function or reduced lung function was more common.

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Author contribution

Dr. Al Obaidy: Study conception, critical revision and study design. Dr. Al-Ani: Acquisition of data, analysis, interpretation of data, drafting of manuscript.

Conflict of interest

None.

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