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Diabetes & its Complications

Diabetes Mellitus, HbA1c, and Lung Function: Do they are Related?

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ABSTRACT

Introduction: *Diabetes mellitus (DM) is a chronic disease which frequently found in the world population. Complications of diabetes mellitus can lead to other comorbidities and mortalities. Pathology of its can cause microangiopathy in alveoli which has contribute to restrict lung volume, capacity, and change in pulmonary functions. However, little is known about the mechanisms of lung dysfunction and there is controversial about relation between duration of diabetes, HbA1c, and pulmonary function in patients with type 2 diabetes mellitus.*

Objective: *The objective was to evaluate the correlation between duration of diabetes, HbA1c, and pulmonary function in patients with type 2 diabetes mellitus.*

Methods: *A cross-sectional study was conducted at Somdet Prayannasungworn Hospital, Chiang Rai, Thailand. Forty participants had diagnosed of type 2 diabetes mellitus from physician, both men and women, and aged between 40-70 years old. They were interviewed for demographic data and duration of diabetes and tested HbA1c and pulmonary function tests (PFTs) from trained physical therapist. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and ratio of FEV1 and FVC (FEV1/FVC), and forced expiratory flow at 25-75% (FEF 25-75%) were measured by spirometry. The Spearman Rank Correlation was used.*

Results: *Diabetes duration was statistical significantly negative correlated with forced expiratory volume in one second (FEV1) ($r = -0.323$, p-value<0.05) and forced vital capacity (FVC) ($r = -0.349$, p-value < 0.05) while HbA1c was not correlated with pulmonary function.*

Conclusions: *Diabetes duration was significant associated with pulmonary function reduction in DM patients. However, relationship between HbA1c and pulmonary function in patients with type 2 diabetes mellitus were not found in this study.*

Keywords

Diabetes mellitus, Pulmonary function, HbA1c.

Introduction

Diabetes mellitus (DM) is characterized by chronic hyperglycemia due to absolute or relative insulin insufficiency. Diabetes mellitus is one of the Noncommunicable diseases (NCDs) and metabolic disorders. It is a chronic pathological disease which mostly found in the world population. The incidence and prevalence of diabetes are gradually increasing and prognosis is not well. The World Health Organization (WHO) reported that prevalence of diabetes is about 422 million people (8.5%of the whole world population) and prevalence greater in older (18.3% in > 65 years old) than younger [1]. Diabetes is more common found in Native Americans, African Americans, Hispatic Americans, and Asia Pacific. Moreover, diabetes mellitus is the major health problem and leading causes of other diseases such as blindness, kidney disease, heart disease, stroke, and peripheral vascular disease. The consequences are causes of blindness and end-stage of renal failure.

Diabetes mellitus is categorized into 2 main types: type I diabetes (Insulin-dependent diabetes mellitus or IDDM) and type II diabetes (Noninsulin-dependent diabetes mellitus or NIDDM).

The type I diabetes is caused by beta cell destruction and usually leading to absolute insulin deficiency while type II diabetes is caused by insulin resistance of peripheral tissue and defective insulin secretion. Approximately 5 to 10 % have type 1 and 90 to 95% have type II diabetes mellitus in the United States [2]. The contributing factors of DM are physical inactivity, other underlying disease, and obesity especially in adults who have BMI more than 25 kg/m2. Recent study found that type 2 diabetes correlated with the obesity, metabolic syndrome, and physical inactivity [3].

The common signs and symptoms of DM are polyuria, polydipsia, dry mouth and itchy skin, blurred vision, hunger and fatigue. Diabetes can cause many chronic complications such as macrovascular disease (stroke and cardiovascular disease), microvascular disease (eye disease and kidney disease), and peripheral neuropathy.

A pathophysiological mechanism of diabetes mellitus can effect to the lung function and adverse reaction. A previous review article revealed that lung may be the target organ of diabetes which involved with microvascular complication especially in lungs [4]. Stratton et al in 2000 found the association between HbA1c and macrovascular and microvascular complications in patients with type 2 diabetes [5]. As same as Sinha S et al. in 2004 found that hyperglycemia affected to the change of collagen and elastin which are the main components of basement membrane and these lead to microangiopathy [6]. A microangiopathy involved with arteriole and tissue surrounded alveoli. A thickening of basement membrane in arteriole caused the limitation of lung capacity and gas exchange in alveoli [7].

In the recent study, Zineldin MA et al in 2015 found that patients with type 2-diabetes had a restrictive respiratory defect and glycemic levels and duration of disease are probably determinants of lung pathology [8]. Moreover, pulmonary disease caused by diabetes can occur in diabetes patients such as pneumonia, asthma, pulmonary fibrosis, and pulmonary tuberculosis. When compared with healthy subjects, patients with type I or type II diabetes are at increased risk for respiratory tract and the risk of further repeated occurrence of common infections [9,10]. The possible mechanism of diabetes lung injury might be diabetic hyperglycemia which affected to glycation, protein glycation (PKC) pathway, NF-KB pathway, polyol pathway, and oxidative stress [11]. However, there are controversial about the relationship between lung function and diabetes. Thus, the objective of this study was to evaluate the correlation between DM duration, HbA1c, and pulmonary function in patients with type 2 diabetes mellitus.

Methods

Design and participants

A cross-sectional study was conducted. Forty participants were recruited from Noncommunicable disease (NCD) clinic, Somdet Prayannasungworn Hospital, Chiang Rai, Thailand. All patients were diagnosed as type II DM from the physician. The inclusion criteria are diagnosed as type II diabetes from the physician, aged between 40 to 70 years old, both male and female, and measured HbA1c no longer than 1 year before this study.

The patients with current smoker, represented signs and symptoms of nausea or severe vomiting, cardiopulmonary disease, hemoptysis, untreated pneumothorax, unstable cardiovascular or vital sign, aneurysm, recent eye, thoracic, and abdominal surgery, active pulmonary tuberculosis, pregnant, systemic lupus erythematosus (SLE), cervical spinal injury, and respiratory diseases were excluded from this study. An informed consent was obtained from the participants before study. This study was approved by the ethical committee of Mae Fah Luang University, Thailand.

Measurements

Demographic data were included gender, age, height, weight, BMI, medication, underlying disease, and DM duration. The glycated hemoglobin (HbA1c), an overall marker of the average levels is over a period of 2-3 months, is measured by blood sample. A spirometry, a standardization test for pulmonary function test, was used by physical therapist that has been trained for the pulmonary function test. The forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and ratio of FEV1 and FVC (FEV1/FVC) and forced expiratory flow at 25-75% (FEF 25-75%) were measured by spirometry, Micro lab, ML3500.

Statistical analysis

Descriptive statistics was used for demographic data. Shapiro-Wilk test was used to test of normality. Spearman Rank Correlation was used to evaluate the correlation between diabetes duration, HbA1c, and pulmonary function. SPSS version 20 was used to analyze the data. The differences were considered significant at p-value < 0.05. Values are expressed as means ± S.D. or as percentage of values.

Results

Baseline characteristics

Forty patients with type II diabetes mellitus (male/female: 23/17) participated in this study. They were 45-72 years old (average 58.45 ± 7.31 years old). They had average BMI 25.72 ± 3.15 kg/m2 and had been estimated as obese grade I [12]. Most of them (80%) had been diagnosed as type II DM for more than 10 years. Moreover, HbA1c value was reported more than 6.5% in 31 patients from the total patients and it was interpreted as hyperglycemia. The underlying diseases which found in this population were diabetes mellitus, hypertension, dyslipidemia, neuropathy, cardiovascular disease, thyrotoxicisis, and chronic kidney disease. About 45% of all subjects had at least three underlying diseases. Most of medications are drugs for diabetes mellitus (Metformin, Glipizide), drugs for dyslipidemia (Simvastatin), and drugs for hypertension (Enalapril, Amlodipine). Only 5 patients had pulmonary function test as abnormal. All of them were completely achieved the protocol. No participants dropped out from the study. The results were shown in table 1.

Baseline Characteristics		Mean ± SD	p-value
Age (years)		58.45 ± 7.31	0.430
Weight (kg)		64.88 ± 12.13	0.037*
Height (m)		158.35 ± 8.97	0.488
BMI (kg/m^2)		25.72 ± 3.15	0.747
Number of underlying disease (n)	1-2 diseases	22	0.000**
	3-5 diseases	18	
Number of medications (n)	1-2 drugs	6	0.029*
	3-5 drugs	31	
	> 5 drugs	3	
Duration of diabetes (yrs)	< 10 years	32	0.000**
	≥ 10 years	8	
HbA1c (%)	≤ 6.5	10	0.000**
	> 6.5	30	
FEV1 (L)		2.73 ± 0.72	0.134
FVC (L)		3.28 ± 0.84	0.547
FEV1/FVC (%)		83.48 ± 8.06	0.000**
FEF 25-75 %		3.36 ± 1.35	0.811

Table 1: Baseline characteristics of participants (n = 40).
Statistically significant (*p-value < 0.05, **p-value < 0.001).
Abbreviations: FEV1: forced expiratory volume in 1 second, FVC: Forced Vital Capacity, FEV1/FVC (%): Ratio of FEV1 and FVC, FEF 25-75%: Forced Expiratory Flow at 25-75%.

Relationship between duration of diabetes, HbA1c, and pulmonary function

When considered the relationship between duration of diabetes, HbA1c, and pulmonary function in patients with diabetes mellitus, the result showed duration of diabetes and FVC were statistically significant low correlation (r =-0.349, p-value<0.05) while duration of diabetes and FEV1 were statistically significant low correlation (r = -0.323, p-value<0.05). It could be estimated duration of diabetes was inversed with FEV1 and FVC. Moreover, HbA1c and FEV1 were low correlation but no statistically significant (r= -0.091, p-value > 0.05). It might be the relationship between HbA1c and pulmonary function had no statistically significant. The results of relationship were shown in table 2.

Variables	HbA1c (%)		Duration of Diabetes	
	r	p-value	r	p-value
HbA1c (%)	-	-	0.220	0.172
Duration of diabetes (yrs)	0.220	0.172	-	-
FEV1 (L)	-0.091	0.572	-0.323	0.042*
FVC (L)	-0.199	0.218	-0.349	0.027*
FEV1/FVC	0.287	0.072	0.138	0.397
FEF 25-75%	0.217	0.178	-0.202	0.210

Table 2: Relationship between duration of diabetes, HbA1c, and pulmonary function.
Statistically significant (*p-value < 0.05).
Abbreviations: HbA1c: Glycated Hemoglobin, FEV1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV1/FVC (%): Ratio of FEV1 and FVC, FEF 25-75%: Forced Expiratory Flow at 25-75%.

Relationship between duration of diabetes and pulmonary function in patients with diabetes duration less than and more than 10 years

When considered the relationship between duration of diabetes and pulmonary function in patients with duration < 10 years group (n =32) and ≥10 years group (n = 8), the result showed duration of diabetes less than 10 years and pulmonary function test were low correlation but no statistically significant (r = 0.039-0.204, p-value>0.05) as same as duration of diabetes more than or equal 10 years and PFTs were low to moderate correlation but no statistically significant in all variables. It could be estimated the relationship between duration of diabetes and pulmonary function were not found in this study. The results of relationship were shown in table 3.

Variables	Diabetes duration			
	< 10 years		≥ 10 years	
	r	p-value	r	p-value
FEV1 (L)	-0.204	0.263	0.561	0.148
FVC (L)	-0.161	0.378	0.464	0.247
FEV1/FVC	0.039	0.832	0.049	0.909
FEF 25-75%	-0.107	0.560	0.528	0.179

Table 3: Relationship between duration of diabetes and pulmonary function in patients with diabetes duration less than and more than 10 years.
Statistically significant (*p-value < 0.05).
Abbreviations: FEV1= forced expiratory volume in 1 second, FVC = forced vital capacity, FEV1/FVC (%) = ratio of FEV1 and FVC, FEF 25-75% = forced expiratory flow at 25-75%.

Relationship between HbA1c and pulmonary function in patients with type 2 diabetes mellitus

When considered the relationship between HbA1c and pulmonary function in patients with well-control DM group (n =10) and poor-control DM group (n = 30), the result showed HbA1c and pulmonary function were low to moderate correlation but no statistically significant in all variables (r = 0.127 – 0.519, p-value>0.05) in type 2 diabetes patients with well-control (HbA1c ≤ 6.5 %). As same as HbA1c and pulmonary function in type 2 diabetes patients with poor-control (HbA1c > 6.5 %) were low correlation but no statistically significant (r = 0.198 – 0.358, p-value>0.05). It could be estimated the relationship between HbA1c and pulmonary function in patients with type 2 diabetes mellitus were not found in this study. The results of relationship were shown in table 4.

Variables	HbA1c			
	≤ 6.5 %		> 6.5%	
	r	p-value	r	p-value
FEV1 (L)	-0.177	0.624	-0.352	0.057
FVC (L)	-0.388	0.268	-0.358	0.052
FEV1/FVC	0.519	0.124	0.198	0.295
FEF 25-75%	0.127	0.727	-0.300	0.873

Table 4: Relationship between HbA1c and pulmonary function in patients with type 2 diabetes mellitus.
Statistically significant (*p-value < 0.05).

Abbreviations: HbA1c: Glycated Hemoglobin, FEV1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV1/FVC (%): Ratio of FEV1 and FVC, FEF 25-75%: Forced Expiratory Flow at 25-75%.

Discussion

The present study found that diabetes duration was associated with significant reduction in pulmonary function in patients with diabetes mellitus. The result showed diabetes duration and FVC were statistically significant negative moderate correlation ($r = -0.349$, p-value<0.05) while duration of diabetes and FEV1 were statistically significant low correlation ($r = -0.323$, p-value<0.05). It could be estimated that duration of diabetes was inversed with FEV1. Whether the duration increased, pulmonary function test decreased.

As we known, diabetes mellitus affects to systemic circulation and its impairments are penetrating to many organs. Fowler MJ in 2008 reviewed the microvascular and macrovascular complications of diabetes mellitus such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, atherosclerosis, and cardiovascular diseases [13]. Abnormalities in endothelial and vascular smooth cell function contribute to atherosclerosis and its complications. Moreover, in the experimental models of diabetes found that endothelial dysfunction was presented by impaired endothelium-dependent and nitric oxide (NO)–mediated relaxation occurred in cellular [14-16].

Most of diabetes researches were focused on vascular dysfunction, thus little is known about pulmonary impairment in diabetes. The earliest study of Schuyler MR et al. in 1976 found that pulmonary function tests tended to be decreased in patients with diabetes mellitus [17]. The result of this study is accordance with many previous studies. Previous study also revealed FVC and FEV1 was significantly lower in diabetes because other factors such as smoking and airway infections [18]. Dharwadkar et al in 2011 found that FVC decreased in 135 ml, FEV1 in 520 ml, PEFR in 54 L/min and FEV1/FVC in 23.50% in diabetes mellitus compared to control subjects [19]. As same as Nidhi Anand et at in 2017 revealed that the mean value of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and peak expiratory flow rate (PEFR) in diabetic group was lower than non-diabetic (p-value < 0.001) [20]. However, pathogenic mechanisms of pulmonary dysfunction in diabetes remain elusive. Many researches try to explain this possible mechanism as following:

Morphological changes in diabetic lung injury

A histological investigation in 2004 showed the morphological changes occurred in rabbit lung after diabetic induction 3 weeks. They found pulmonary capillary dilatation, severe parenchymal hemorrhage, and clumping of red blood cells was presented in diabetic animals. In pancreas and lung samples, the most dramatic lesions were present in the 3-week diabetic animals [21]. Other investigations also reported that hyperglycemia damages the respiratory system caused by pulmonary interstitial injury and microangiopathy, increase in the volume proportion of alveolar wall and alveoli per unit volume, amounts of collagen, elastin, and basal laminae, and surface to volume ration of rabbit lungs [22,23]. The thickened basal membrane with inflammation reaction is also found. Lungs are exposed to changes induced by oxidative stress in diabetes through NF- B activation and PDTC seems to be useful to prevent diabetic lung injury [24]. Thus, the morphological changes in diabetic lung injury can occur subsequent.

Pulmonary dysfunction in diabetic lung injury

Cross-sectional and longitudinal studies were found decreased lung function in diabetes mellitus. The association between pulmonary function decline and diabetes were statistical significant. When compared with health subjects, patients with diabetes have significant decreases in parameters including decreased in vital capacity, total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1) [20,25,26].

Although there are many possible mechanisms of diabetic lung injury, the relationship between clinical tests and diabetes mellitus were not extensively. There was not found correlation between duration of diabetes, HbA1c, and pulmonary function.

Relationship between duration of diabetes, HbA1c, and pulmonary function

The present study found duration of diabetes and FVC were statistically significant moderate correlation while duration of diabetes and FEV1 were statistically significant low correlation. It is consistent with Copenhagen Heart study in 1989 reported that individuals with diabetes mellitus have a slightly impaired forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), compared with nondiabetic subjects [27]. Subsequently, the longitudinal study of decline of FVC and FEV1 was established in the individuals with type 2 diabetes, 15 years follow up. They found that diabetic subjects have a lower FEV1 and FVC than individuals without diabetes but this deficit seems not to be progressive in the long term [28].

Nevertheless, we found no statistically significant correlation between HbA1c and FEV1 in this study. It is consistent with Shah SH et al in 2013, they found no correlation found between FVC and FEV1 and duration of illness as well as HbA1c [29]. Other studies also support these results [30-32]. It might be that HbA1c levels are indicators of glycemic control for a short period (2-3 months), it was not effected to pulmonary function. While some studies have shown the decline in PFTs was negatively correlated with HbA1c [27,33].

Limitation

The numbers of participants are not equal in duration of diabetes and HbA1c level group. The further study should equally divide for the accurate analysis. Moreover, the investigation of effect of glycated hemoglobin and PFTs should be tested in large population. A linear regression analysis should be used to predict the prognosis of disease.

Conclusion

Diabetes duration was associated with significant reduction in

pulmonary function in patients with diabetes mellitus. It might be estimated that if the duration increased, pulmonary function test decreased. While the relationship between HbA1c and pulmonary function in patients with type 2 diabetes mellitus were not found in this study.

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A.M. wrote the manuscript and research data. C.R. researched data. A.N. contributed to discussion and reviewed/edited the manuscript. P.B. contributed to discussion and reviewed/edited the manuscript. P.K. researched data. A.M. is the guarantor of this work and had full access to all the data in the present study and take responsibility for the honesty and accuracy of the data and data analysis. The author would like to thank physical therapist, nurse, physician, and staffs from Somdet Prayannasungworn Hospital, Chiang Rai, Thailand. We also present the thankful to any suggestion and kindness from our participants.

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