Pulmonary Function Impairment In Diabetic Older Individuals

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Abstract

Introduction: Diabetic individuals have several complications, such as diabetic retinopathy and nephropathy as well as an increased mortality risk and impairment in health-related quality of life. Despite some authors have suggested that pulmonary function reduction might be a chronic complication of *Diabetes mellitus* (DM), there are doubts whether the pulmonary function decrease is really caused by DM itself or if it represents a deleterious impact of ageing process.
Aims: This study aimed to compare respiratory muscle strength and pulmonary function in diabetic and non-diabetic elderly patients as well as to evaluate a possible correlation of this effect with glycemic control.
Methods: For this case-control study, older adults (age over 60 years old) were randomly selected from an ageing study (EELO project) and they were separated in Diabetic (DG) and non-diabetic group (referred as control group, CG). Respiratory muscle strength was assessed by measuring maximum static inspiratory and expiratory pressures (MIP and MEP) using manovacuometer, while pulmonary function was evaluated by spirometry (considering the following variables: FVC, FEV1, FEV_1/FVC). All the variables were presented as % of predicted values, corrected for Brazilian population.
Results: 255 older adults were enrolled at this study (85 diabetic and 170 non-diabetic patients). Diabetic individuals presented lower MIP (p=0.03), FVC (p=0.02) and FEV_1 (p=0.02) when compared to non-diabetic individuals. However, no differences were observed concerning MEP and FEV_1/FVC between the groups. Positive correlations between glycemic control and FVC (rS: -0.14; p=0.02) and between glycemic control and FEV_1 (RS: -0.16; p=0.01) were observed according to Sperman Correlation.
Conclusion: According to these results, it can be concluded that diabetic patients show respiratory muscle weakness and decline of pulmonary function in comparison to non-diabetic individuals. Therefore, it can be suggested that pulmonary function evaluation should be recommended at the evaluation of diabetes' chronic complications.

Keywords: Elderly; Diabetes; Pulmonary function; Respiratory muscle strength.

INTRODUCTION

The type-2 *Diabetes mellitus* (DM) is a prevalent disease worldwide, affecting approximately 25% of the elderly population [1], with a projection of about 300 million adults by 2030 [2].

DM patients have several complications, such as obesity, retinopathy and nephropathy [3] as well as an increased mortality risk and impairment in health-related quality of life, representing high costs to health system [4]. Thus, creating effective policies towards the disease treatment is considered a challenge for public health system.

Diabetic individuals also have higher muscle mass loss [5] and reduced muscle strength as well as less tolerance to exercise when compared with non-diabetic patients [6-9].

Regarding respiratory muscle strength, clinical observation indicates that DM is associated with a higher risk of developing respiratory muscle weakness [7-9]. Recent studies with animal models showed that diabetes evokes severe damage to the diaphragmatic function, leading to a substantially reduced respiratory muscle capacity [10].

Besides, several studies have described an association of pulmonary function and DM [11-13]. There are evidences that the deterioration of glycemic

control is a strong determinant of reduced pulmonary function in type-2 diabetic patients [14,15].

Additionally, Ljubic et al.[16] showed that diabetes presence could lead to pulmonary complications, due to collagen and elastin changes [17]. Therefore, despite some authors have suggested that pulmonary function reduction might be a chronic complication of DM, there are doubts whether the pulmonary function decrease is really caused by DM or if this represents a deleterious impact of ageing process.

Thus, this study aimed to compare respiratory muscle strength and pulmonary function in diabetic and non-diabetic elderly patients as well as to evaluate a possible correlation of this effect with glycemic control.

METHODS

This study was approved by the University Research Ethics Committee (Protocol no. PP0063/09). Individuals were informed about the aims of the study and signed the informed consent prior to any methodological procedure.

This case-control study followed the criteria established by Strengthening the Reporting of Observational Studies in Epidemiology – STROBE[18]. The convenience sample consisted of older adults (age over 60, according to recommendations of World Health Organization for developing countries[19]) who participated on an interdisciplinary project (EELO Project - Study on ageing and longevity). The EELO Project is a thematic project developed at University of Northern Parana (UNOPAR) which aimed to evaluate the socio-demographic factors and indicators of health conditions of older adults in Londrina, a city of Northern Paraná, Brazil. The total sample of the EELO project consisted of 508 individuals, which is representative of the 43610 citizens older than 60 years living in Londrina.

This study was developed in Londrina, a middle-sized city from south region of Brazil since the elderly population of this city represents 12% of the total population with similar prevalence described in other developed countries [20,21].

Individuals with type-2 DM who met International Classification and Diagnosis Standards for Diabetes classification[22] were included at the diabetic group (DG). Patients were classified as diabetic if they exhibited the following symptoms: polyuria, polydipsia and weigh loss associated with glycemia above 200 mg/dl [23]. All patients were under proper medical treatment with oral antidiabetic drugs or insulin, as necessary. Moreover, health older individuals without diabetes were recruited as a control group (CG).

Pulmonary diseases, thorax abnormalities, smoking history, cardiac insufficiency disease or treatment, respiratory infection over the last 30 days and previous or actual smoking were established as the exclusion criteria for this research. After analysis of eligibility criteria, 255 individuals were included (85 diabetic patients referred as the diabetic group and 170 non-diabetic patients referred as the control group).

Structured questionnaires were used to assess data regarding anthropometric and diseases characteristics and medication consumption.

All blood samples were collected by peripheral vein puncture after 12-hour fasting. Fast glycemia was measured by colorimetric enzymatic methodology (Lab test kit) and glycated hemoglobin (HbA1c) through HPLC Biorad-D10 Hemoglobin Testing System. Diabetic patients were classified as controlled and uncontrolled diabetes, according to the value of glycated hemoglobin (Table 1). Glycated hemoglobin is a marker that reflects the glycemic control in a period from 8 to 12 weeks previously to the exam[24].

Table 1 – Criteria of glycemic control according to HbA1c levels.

Classification	HbA1c (%)
Non-diabetic individual	4.0 to 6.0
Controlled Diabetic individual	5.7 to 6.4
Uncontrolled diabetic individual	≥ 6.5

HbA1c = hemoglobin A1c

The patients' respiratory muscle strength was evaluated through the measure of the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using the GERAR® analog manovacuometer (São Paulo, Brazil) featuring a -200 to + 200 cmH_2O scale, a capsule-type sensor and a spigot connection. The exams attended international standards established by the American Thoracic Society [25], previously described by Black and Hyatt [26]. There were performed at least 3 maneuvers, being 2 reproducible (difference lower than 10% between values).

The highest value of respiratory muscle strength (MIP and MEP) found was used and expressed in percentage of predicted values (pred.) described for Brazilian population, according to the Neder et al [27].

Pulmonary variables (forced vital capacity (FVC), forced expired volume at the first second (FEV_1), FEV_1/FVC ratio) were measured by Pony-FX spirometer (COSMED, SRL, Rome, Italy).The exams attended international standards established by the American Thoracic Society and the European Respiratory Society [28].

Spirometry was performed at controlled temperature room. The subjects took a rest from 5 to 10 minutes before the test and during this period, they remained sited and using a nose clip. Before the procedure started, it was carefully described. The spirometer was computerized and printed the FEV_1 and FVC values after the forced expiration had been performed. Best of three satisfactory readings was taken for the analysis. The highest value for FVC and FEV_1 were used in the ratio FEV_1/FVC. The variables were shown as the percent predicted values based on regression equations for Brazilian population [29].

GraphPad Prism 5.0 and G Power 3.0 were used for statistical analysis, setting the confidence interval in 95% and 5% of the significance level ($p<0,05$) for all tests.

A pilot study was developed to calculate the sample size for testing the null hypothesis that there is no difference between MIP and the MEP and the pulmonary function between the diabetic and the non-diabetic groups. The following statistic parameters were established (power test: 0.8 and p<0.05) and it was determined that the minimum needed sample for this research would be 56 diabetic patients and 112 non-diabetic ones.

Shapiro-Wilk test was used to evaluate whether the data had normal distribution. Considering that the variables used did not show normal distribution, all data were presented as median and interquartile range [25-75].

Mann-Whitney test was used to compare variables related to respiratory muscle strength MIP and MEP, as well as those related to pulmonary function (FVC, FEV1, FEV1/FVC) between the groups. Besides, Spearman Correlation was used to evaluate possible associations between glycemic control and the variables studied.

RESULTS

Initially, the study was composed by 455 individuals. However, 255 attended the eligibility criteria and composed the final sample (85 diabetic patients and 170 control patients) and 200 older adults were excluded.

The diabetic group had similar age (Mean: 70.12±6.85) than the control one (Mean: 69.55±6.32), according to the Student t test (p=0.50). Both groups had similar anthropometric data expressed in table 2.

Table 2 – Anthropometric data of the groups.

Anthropometric data	DG	CG	p
Gender (M/F, %)	35.8/ 54,2%	33.7/63.3%	0.73
Race (White /Non-white%)	60.5/ 39.5%	63.20/ 36.80%	0.68
Age (anos)	70.09 ± 6.96	69.58± 6.29	0.55
Height (cm)	158.04 ± 8.88	157.06 ± 8.15	0.37
Weight (Kg)	69.45 ± 12.53	65.92 ± 12.38	0.05
BMI	27.8 ± 4.48	26.67 ± 4.35	0.06

DG = diabetic group; CG = control group; M = male; F = female; BMI = body mass index.

Diabetic individuals presented lower MIP (DG: 81.9% pred.; Interquartile interval range: 71.2 – 110.3) when compared to non-diabetic individuals (CG: 95.2% pred; Interquartile range: 74.8 – 119.5), according to the Mann-Whitney test (p=0.03).

There was no difference in the MEP of diabetic (DG: 102.8% pred; Interquartile interval: 80.5 – 130.8) and non-diabetic patients (CG: 108.9% pred; Interquartile interval: 89 – 137.1), according to the Mann-Whitney test (p=0.06). Data concerning inspiratory and expiratory muscle strength is shown in table 3.

Forced vital capacity (FVC) was lower in diabetic individuals (GD: 75.5% pred; Interquartile interval:67.9 – 86.9) when compared with non-diabetic ones (CG: 82.63% pred; Interquartile interval: 73.6 – 94.2), according to the Mann-Whitney test (p=0.02).

Forced expired volume at the first second (FEV_1) was also lower in diabetic individuals (DG: 79.15% pred; Interquartile interval: 66.59 – 90.12), in relation to non-diabetic ones (CG: 85.36% pred; Interquartile interval: 71.74 – 97.06), according the Mann-Whitney test (p=0.02).

The relation FEV1/FVC did not present meaningful differences between the diabetic and the non-diabetic group (DG: 103.1; Interquartile interval: 93.35 – 109.3 *versus* GC: 102.2; Interquartile interval: 94.91 – 107.7), according to the Mann-Whitney test (p=0.45). Data concerning pulmonary function evaluation is also shown in table 4.

Table 3 – Respiratory muscle strength evaluation.

Variables	DG	CG	p
	Median (1°. Q. – 3°. Q.)	Median (1°. Q. – 3°. Q.)	
MIP (% pred. value)	81.9 (71.2 – 110.3)	95.2 (74.8 – 119.5)	0.03*
MEP (% pred. value)	102.8 (80.5 – 130.8)	108.9 (89 – 137.1)	0.06

DG= diabetic group; CG= control group; MIP= maximal inspiratory preassure; MEP= maximal expiratory preassure; 1°.Q.= first interquartile interval; 3°.Q.= third interquartile interval.
* statistically significant, Mann-Whitney's test, p<0,05.

Table 4 – Pulmonary function evaluation.

Variables	DG	CG	p
	Median (1°. Q. – 3°. Q.)	Median (1°. Q. – 3°. Q.)	
FVC (% pred. value)	75.5 (67.9 – 86.9)	82.63 (73.6 – 94.2)	0.02*
FEV_1 (% pred. value)	79.15 (66.59 – 90.12)	85.36 (71.74 – 97.06)	0.02*
FEV_1/FVC (%)	103.1 (93.35 – 109.3)	102.2 (94.91 – 107.7)	0.45

DG = diabetic group; CG = control group; FVC = forced vital capacity; FEV_1 = forced expiratory volume at the first second; FEV_1/FVC = ratio between FEV_1 and FVC; 1°.Q. = first interquartile interval; 3°.Q. = third interquartile interval.
* statistically significant, Mann-Whitney's test, p<0,05.

DISCUSSION

The present study provides strong evidence that the pulmonary function is impaired in type-2 diabetic individuals. Although it was observed a marked reduction of the MIP on the diabetic group, the same decline was not detected on MEP. These results may be explained by the fact that abdominal muscles are known for their substantial contribution to the exhaling pressure, whilst inhaling pressure essentially depends on the diaphragm muscle [30,31]. Similarly, individuals with type-1 diabetes showed lower respiratory muscle strength [32,33] and decreased muscle endurance[34] in opposition to non-diabetic individuals. However, Kabitz et al.[15] did not verify changes in pulmonary function of type-2 diabetes patients.

Despite there are some reports concerning peripheral muscular weakness in diabetic individuals[5;35;36], few studies investigated pulmonary function in such patients.

The forced vital capacity (FVC) and the forced expired volume at the first second (FEV_1) were lower in diabetic group in comparison to the non-diabetic one. These data are in agreement with previous studies [37-41]. Despite the significant reduction of FVC and FEV_1, it was not observed a statistically significant decline of

the relation FEV_1/FVC (p=0.45), confirming previous reports[16;39].

Considering that DM induces metabolic and structural changes on skeletal muscles, many mechanisms may contribute to the occurrence of respiratory muscle weakness found in diabetic individuals. Indeed, DM causes metabolic changes characterized by reduced cellular glucose caption as well as oxidation of fatty acids and structural changes, with muscular atrophy, increase of lipids stockage, as well as changes in muscle fibers [42].

Additionally, studies have shown that an increase of systemic inflammation associated to diabetes[35] could result in pulmonary inflammation[43] as well as causing wounds in the respiratory tract [35, 44]. Besides, a decrease in respiratory defense mechanisms and an increase in the susceptibility to oxidative profile may result in subsequent loss of the pulmonary function[4]. Furthermore, it was demonstrated that pulmonary complication in diabetic patients are, partially, due to a narrowing in alveoli walls, alveolar capillaries and pulmonary arterioles [45, 46].

Moreover, it is noteworthy that microvascular complications and hyperglycemia may occur by glycosylated pro-inflammatory protein formation [47]. Considering that the alveolar-capillary network consist of a large network, the lungs can be potentially affected by diabetic microangiopathy[48,49].

There are evidences that pulmonary alterations, as well as muscle, renal and retina changes observed in diabetic patients are related to a poor glycemic control. In this context, Yeh et al.[40] reported that observed changes in FVC and FEV_1 are related to the degree of hyperglycemia, diabetes' duration and pharmacological treatment.

The association of DM and the impaired pulmonary function may occur in a bidirectional way. Although various studies have reported pulmonary alterations as one of the chronic complications of DM, it was also observed that individuals with lower pulmonary function present risk of developing insulin resistance and type-2 diabetes. Besides, it was also observed that subjects with impaired result at spirometry tests presented higher risk for DM [7;11;35; 50; 51].

It can be pointed as one of the study limitations the lack of evaluation of lung diffusion of carbon monoxide capacity (D_{CO}) that may also be reduced in diabetic patients [40]. Furthermore, it may be highlighted that longitudinal studies should be performed to evaluate the pulmonary function in diabetic elderly.

However, the novelty in this study was the assessment of respiratory muscle strength and pulmonary function at the same older individuals. In addition, changes in lung function were due to poor glycemic control of diabetes.

From the results, it can be concluded that diabetic patients show respiratory muscle weakness (expressed through MIP) and decline of pulmonary function (expressed through FVC and FEV_1 levels) in comparison to non-diabetic individuals. Additionally, it was also observed that the impairment in pulmonary function is related to glycemic control in physically independent elderly.

Considering that DM is an important public health problem, with high prevalence and morbidity, it can be suggested that pulmonary function evaluation could be recommended at the evaluation of diabetes' chronic complications.

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