LITERATURE REVIEW

DIABETIC PNEUMOPATHY

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Abstract

Introduction: Diabetes mellitus is a condition whose main characteristic is excessive blood glucose and, if not controlled, can cause chronic systemic complications such as, nephropathy, pulmonary dysfunction, retinopathy and vascular disorders, among others. Lung complications in diabetics, due to chronic hyperglycemia, have been studied more recently. Objective: This study aims to conduct a literature review on changes in lung function in diabetes mellitus, through an integrative bibliographical review. Method: Bibliographic survey, through an integrative literature review, to establish a correlation between glycemic control and lung function in diabetic subjects. The integrative review was made by searching the Medline international databases for review of manuscripts. Selection of these databases was based on the wide range of journals covered by each of them and our goal was to provide an overview of the scientific production devoted to the topic over the timeframe of analysis. The following inclusion criteria were considered during the review: use of the keywords "lung" OR "pneumopathy" OR "lung disease" MeSH "diabetes mellitus" entered into the search form, and availability of an abstract in English. Results: A total 12 scientific productions were selected by contain information about the pulmonary function alterations in diabetes. Conclusion: The main pulmonary function abnormalities found in diabetics are: lung volume reduction; lung elasticity reduced; capillary blood volume reduction; thickening of the capillary basement membrane; decrease in muscle strength; and paresis or bilateral diaphragmatic paralysis due to phrenic neuropathy.

Keywords: Diabetes mellitus; Lung; Lung diseases.

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INTRODUCTION

Diabetes mellitus (DM) is a disease whose main characteristic is excessive blood glucose and, if not controlled, can cause chronic systemic complications such as renal, pulmonary, and ocular vascular disorders and others. Diabetes type 2 (DM_2) has affected more than 217 million people worldwide, and it's expected to become more and more prevalent in the future.[1] According to the World Health Organization (WHO), it is estimated that about 366 million people will have DM by the year 2030.[2]

The DM is classified into type 1 diabetes (DM_1), DM_2, gestational diabetes (GD) and other specific types. In the DM_1 onset the beta cells are destroyed, usually leading to a complete deficiency of insulin. When it comes to the DM_2, there are various degrees of decrease in insulin secretion and resistance, this being the most common type [3] and related to genetic and environmental factors.[4] The GD happens when there is a decreased carbohydrate tolerance, being first diagnosed during pregnancy and may or may not remain as a metabolism defect after giving birth.[5] In specific types of diabetes genetic defects of beta cell function or insulin action, diseases of the pancreas, endocrinopathies, drug or chemical induction products, infections and unusual forms of immune-mediated diabetes are involved.[3]

The DM is a debilitating and devastating chronic disease that affects many organs, including the lungs. The incidence and prevalence of DM and its complications have been increasing significantly. Pulmonary complication in diabetic patients, resulting from chronic hyperglycemia that causes glycation end leading to the formation of fibrotic tissue of the bronchial tree has been studied.[6]

Along with the increased protein catabolism, there is a decrease in respiratory muscle strength and metabolic disorder that leads to neuropathy of the phrenic nerve, which may cause diaphragmatic paralysis. Thus, the DM causes reduced respiratory function, like thickening of the basement membrane by reducing the glycation gas diffusion ability. Besides the glycation of immunoglobulin and increased chance of acute and chronic pulmonary infections which causes parenchymal fibrosis with consequent reduction the mechanical lung, the hyperglycemia causes the local biochemical changes in the lungs and reduces the antioxidant defense in the lungs. The consequence of local oxidative stress reduces lung volumes, elasticity and bronchodilation. Hence, the DM plays a significant role in the development of pulmonary complications in addition to the kidney, retinae, nerve and vessels.

Based on the above, this study is going to conduct a literature review, through an integrative bibliographical review, to establish a correlation between glycemic control and lung function in diabetic subjects.

METHODS

SAMPLE DELIMITATION

An integrative review was made by searching the Medline international databases for review of manuscripts. The Medline is taken to be one of the largest medical literature databases in the world, and the Medical Subject Heading (MeSH) descriptor for Medline. These keywords produced results specific to documents using the terms which are described below. The selection of these databases was based on the wide variety of indexed medical journals, and our goal was to provide an overview of the scientific production devoted to the topic over the timeframe of analysis.

Bibliographic survey through an integrative literature review to establish a correlation between glycemic control and lung function in diabetic subjects. The integrative review was made by searching the Medline international database for review of manuscripts. Selection of these databases was based on the wide range of journals covered by each of them and our goal was to provide an overview of the scientific production devoted to the topic over the timeframe of analysis. The following inclusion criteria were considered during the review: use of the keywords "lung" OR "pneumopathy" OR

"lung disease" MeSH "diabetes mellitus" entered into the search form, and availability of an abstract in English.

RESULTS AND DISCUSSION

A total 12 scientific productions were selected by contain information about the pulmonary function alterations in diabetes.

PULMONARY EFFECTS OF DIABETES MELLITUS

The metabolic, hormonal and microvascular disturbances frequently leads to kidneys, retinae, nerves and cardiovascular system compromise by DM, with no uniform standard for tissue involvement in diabetic patients.[7]

The lung is also a target organ for diabetic microangiopathy, both in DM_1 and in DM_2. The pathogenesis of late diabetic complications on the lungs is related to the emergence of angiopathy and the synthesizer of nonenzymatic glycosylation tissue proteins, which leads to accumulation of advanced glycosylation end products.[8]

In the anatomical point of view, when we observe the lungs parenchyma, we find that the functional lung unit, the alveoli, which will ensure adequate ventilation and hematosis for oxygen (O_2) can be distributed around the body. Electron microscopy shows the anatomical structure with a dense capillary network surrounding the alveoli and entire pulmonary structures to facilitate gas exchange.

One of the first studies which assessed the issue related to pulmonary changes in diabetics was published in 1999.[9] As the long evolution of DM is characterized by diffuse alterations of the basement membrane, based on this premise it is needed to determine whether the lung also features basal membrane such as other organs like the kidneys. Although this study was conducted with a small n sample size, the goal was to evaluate the basement membrane thickening in the lungs of diabetic patients, check whether this thickening is found throughout extension or is restricted to some specific areas and compare the thickening of the basal membrane to the kidney'. The material was obtained from autopsies of six diabetics and six nondiabetic controls, harvested up to nine hours after death. The electron microscopy demonstrated that the controls' both basal endothelial and renal tubular basement membrane were thinner than in diabetics'. Thus, this study demonstrated that in diabetics there is a thickening of the kidney basement membrane such as in the lungs', with a similar magnitude in both. The study also demonstrated that all lung regions are equally affected, however, contrary to what was observed in the kidneys, there was no correlation between the lung basement membrane thickening and the duration and type of DM.

One of the consequences of structural changes in the diabetic lung is the increased pulmonary alveolar-capillary barrier, leading to gas exchange impairment.[10] Thus, there is reduction in diffusion of O_2, which can be assessed in the laboratory through the diffusion of carbon monoxide (CO), a mechanism very similar to that of the O_2, assessed through plethysmography.

It must also be noted that the lung tissue plays an extremely important role in lung elasticity, thus any changes in this tissue, as occurs very frequently in DM, will imply in changes in the lung function. The strength and stability of the lung tissues are supported by collagen and elastin fibers bound together through cross-linking.[11]

The elasticity and lung function require all tissue elements working in harmony on their proper spatial orientation. Thus, changes in collagen and elastin can significantly alter their functionality.[12] Therefore, changes in the basal membrane of the alveolar epithelium and alveolar capillaries, changes in connective tissue's biochemical level and changes in the chest's autonomic nervous system result in changes in lung mechanics.

Until recently, only lung conditions frequently occurring in diabetic such as fungal infections, tuberculosis, and pneumonia, were discussed, and the appropriate control together with appropriate treatment seemed to reduce this risk.

[13] Currently, it is observed that even in the absence of manifestations of lung disease such as asthma, chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis, the studies reported pulmonary function changes in diabetic subjects.[14] Therefore, in situations where hyperglycemia is present, lung function tends to deteriorate over time, pointing the lung as eventual and probable target organ for diabetic complications as well as kidney, retinae and nerves.

ROLE OF PULMONARY FUNCTIONAL TESTING IN DIABETIC

Studies of lung function in diabetics have become frequent after the release of inhaled insulin, and from then on knowledge of lung function in diabetic patients has evolved significantly.

LUNG TESTING

1. Spirometry

Spirometry is the most reproducible, standardized, and objective way to measure the obstruction of airflow for the diagnosis and treatment of COPD.[15] Spirometry was first described by John Hutchinson in 1846, and is the oldest assessment tool still being used in clinical trial. It measures volume and airflow, especially the slow vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and their interactions (FEV_1/VC and FEV_1/FVC). Through these, one can diagnose the presence and severity of airway obstruction[16,17] and evaluate the risk of COPD, lung cancer, coronary heart disease and stroke.

FEV_1 is the volume of air that can be exhaled from the lungs in the first second of a forced expiratory maneuver, FEV_1 evaluates obstructive disorders.

The FVC is the total volume of air that is expired after a maximal inspiration. When the lung loses its elasticity, this is one of the first parameters to display change. It is an important maneuver to measure restrictive lung disease.

The FEV_1/FVC is the one that better evaluates the presence of obstructive and restrictive disorders. When there is a change in FEV_1 and FVC and the result of this ratio is less than 0.8, the patient is considered to have an obstructive lung disease. Whenever the ratio reaches a value greater than 0.8 it is a restrictive lung disease.

It is important to conduct spirometry in diabetics because the DM and DM1 in particular might cause lung volume reduction due to changes in lung elasticity.[18]

2. Plethysmography

Plethysmography is a pulmonary function test that evaluates lung volumes in a more detailed manner than spirometry as these measurements provide essential information for the characterization of present disturbances due to respiratory diseases.

Plethysmography is indicated to diagnose restrictive lung disease; to evaluate obstructive pulmonary diseases, such as bullous emphysema and cystic fibrosis; to track the course of disease and response to treatment; to assess the resistance to airflow, the response to bronchodilators and whether the lung capacity will be affected by treatments such as methacholine, histamine or isocapnic hyperventilation. Although lung plethysmography cannot determine the etiology of the disorder, it may help reduce the effects such as the destruction of lung structure and disruptors on the chest wall muscles which would cause inability or difficulty to expand and contract the lungs.

3. Carbon monoxide diffusion

The test of the diffusing capacity of the lung for carbon monoxide (DLCO) is one of the most clinically valuable tests for evaluation of pulmonary function. The DLCO capacity is designed to reflect the properties of the alveolar-capillary membrane, especially the ease with which it moves from O_2 inhaled into the red blood cells in the pulmonary capillaries. The absorption of most soluble gasses (such as nitrous oxide or acetylene) is limited by

pulmonary blood flow. In contrast, the strong affinity of hemoglobin to CO, combined with massive red cell's ability to absorb CO, causes the CO absorption to be less dependent from cardiac output.

Associated with the basic tests, DLCO is indicated for evaluation and tracking cases of COPD and of restrictive diseases, providing insight on whether the restriction is related to extra pulmonary changes or intrapulmonary causes; preoperative evaluation of pulmonary resection; disability assessment and to identify the need for oxygen therapy.

PULMONARY EVALUATION STUDIES IN DIABETIC PATIENTS

The association between DM and lung function has resulted in inconsistent outcomes in several published studies.

A meta-analysis of 3,182 diabetic patients without lung disease compared with 27,080 control subjects was performed to investigate the association between DM and lung function.[19] In the study design 40 articles of the 1,280 evaluated were selected. In this study FEV_1, FVC and DLCO have been assessed. The results showed that there is a statistically significant pulmonary dysfunction in individuals with DM, indicating a predominant restrictive pattern. These results were independent of body mass index (BMI), smoking, DM evolution time and glycosylated hemoglobin levels (HbA1c). The association of pulmonary dysfunction seems to be more evident in DM_2 than in DM_1 and given the relatively high frequency of DM in COPD it is tempting to speculate that a poorly controlled DM could enhance the progression of COPD. As the results of this study refer to a subpopulation of diabetics without apparent lung disease, it would be important to investigate the potential implications of those diabetics who have a concomitant diagnosis of asthma, COPD or heart failure. Individuals with left ventricular failure have a reduced DLCO due to thickening of the pulmonary capillary membrane frequently resulting in lung edema, thereby also worsening of O2 diffusion, complicating the overall clinical condition of these individuals

Another interesting study assessed the interaction between glycemic status and lung function.[20] The study was conducted in 3,254 participants of the Framingham Heart Study to evaluate the interaction between DM and fasting glucose levels in lung function. The study subjects were classified as current smokers, former smokers, and nonsmokers. The results showed that both FEV_1 and FVC were lower in diabetic patients than in non- diabetics. It was also shown that there is a parallel between former smokers and hyperglycemia compared with those who never smoked. Additionally, smokers' blood glucose levels were perceived to be much higher. The study concluded that both the DM and hyperglycemia were associated with reduced lung function, represented by the concomitant decrease in FEV_1 and FVC. The fact that this effect is greater in smokers suggests an interaction between fasting glucose levels and smoking.

There was few information between the association of passive smoking or changing smoking habits over time and DM. Therefore, a study examined the association between passive smoke exposure, active smoking and the risk of DM_2 in women.[21]. This is a prospective study of 102,526 women in the Nurses' Health Study who did not have DM in 1,982 and who had a segment for 24 years. In the segment of the study were 5,392 cases of DM_2 identified. The passive smokers had a significantly increased risk of progression to DM_2. The risk for DM was also significant for former smokers. Current smokers had a higher risk of an incident of DM_2. The study concludes that active smokings and passive smoking are associated positively and independently to the risk of DM_2.

A case-control, longitudinal and observational study to evaluate pulmonary function in individuals who developed DM_2 and healthy ones over a period of nine years had important results regarding that topic.[22] They assessed lung function in both the cases and the controls in three phases: before the diagnosis of DM_2, right after the diagnosis of DM_2 and after wards during follow-up.

It has been observed that diabetics had FEV_1 and FVC levels reduced in all the three situations, even when adjusted for age, height, weight and smoking.

This study concludes that men are more likely to develop DM, displaying a reduction in lung function compared to those who did not develop DM. The study postulates that the mechanisms involved in insulin resistance may be responsible for decreased lung function over time.

The smoker lung displays an increased concentration of TNF-α and interleukin-6 caused by the inflammatory process.[23] These proinflammatory cytokines in the liver increased C reactive protein production, an important marker of inflammation involved in the metabolic syndrome and DM.[24]

Another study to assess lung function in diabetics with and without COPD was conducted and presents results from a database comprised of 10,129 participants in the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) Study.[25] In that study, lung function was assessed by specific protocol and multivariate models of lung function within the COPD stages - GOLD (Global Initiative for Chronic Obstructive Lung Disease) - controlling age, sex, current stage of smoking, ethnicity and BMI.

The GOLD for COPD was classified into four stages : GOLD 1 = Mild, FEV_1 / FVC <70 % FEV_1> 80% predicted; GOLD 2 = Moderate, FEV_1 / FVC <70 % FEV_1 ≥ 50% and ≤ 80% predicted , with or without symptoms (cough, sputum); GOLD 3 = Severe, FEV_1 / FVC <70 % FEV_1 ≥ 30% and ≤ 50% predicted, with or without symptoms (cough, sputum); GOLD 4 = Very Severe, FEV_1 / FVC <70 % FEV_1< 30% predicted, the presence of respiratory failure or right heart failure signs; GOLD U: Undefined, FEV_1 / FVC ≥ 70 % , FEV_1<80 %.[26] The results showed that participants with DM have reduced function after controlling for known risk factors and also showed significant reductions in exercise capacity and quality of life through functional stages of COPD, suggesting an important role in pulmonary vascular angiopathy higher than the BMI.

CONCLUSIONS

Based on the studies described, the most consistent pulmonary function abnormalities found in diabetics are: lung volume reduction; reduced lung elasticity in both children and adults who attend with low FVC; diffusing decreased due to reduction in capillary blood volume and thickening of the capillary basement membrane; decreased muscle strength; paresis or bilateral diaphragmatic paralysis due to phrenic neuropathy, which may explain dyspnea and even orthopnea arising in some diabetics and peripheral airway dysfunction in DM_1 even in the absence of smoking or COPD. Individuals with DM1 are the ones who have reduced lung elasticity. In addition, the smoking in diabetic patients is an increased risk for onset of COPD when compared to non-diabetic patients

FINAL CONSIDERATIONS

It is suggested that physicians, during the anamnesis of patients with DM should inquire about smoking needs. That would be a way to assess the necessicity to, perform spirometry and, if there is an FVC below 70 %, the examination should then be continued with plethysmography DLCO. Remember that the presence of COPD or heart failure in DM patients may further accentuate the fall of DLCO.

It also emphasized that the increase in HbA1c is associated with reduced lung function, as poor self- glucose regulation is associated with poor lung function.

From the above, it is inferred that DM is associated with the following pulmonary complications: infection, pulmonary edema, sleeping respiratory disorders, reduced lung elasticity, decreased CO diffusion, reduction of branchiomotor tone, increased risk of thromboembolism due to hypercoagulable state, higher prevalence of pulmonary hypertension. Besides that, smoking in diabetics puts the patient at agreater risk of COPD when compared with non-diabetic subjects .

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