



Looking for solutions to lung dysfunction in type 2 diabetes

Rafael Simó^{1,2}, Albert Lecube^{2,3}

¹Endocrinology and Nutrition Department, Hospital Universitari Vall d'Hebron, Diabetes and Metabolism Research Unit, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain; ²Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; ³Endocrinology and Nutrition Department, Hospital Universitari Arnau de Vilanova, Obesity, Diabetes and Metabolism Research Group (ODIM), Institut de Recerca Biomèdica de Lleida (IRBLleida), Universitat de Lleida, Lleida, Spain

Correspondence to: Rafael Simó, MD, PhD. Endocrinology and Nutrition Department, Hospital Universitari Vall d'Hebron, Diabetes and Metabolism Research Unit, Vall d'Hebron Institut de Recerca, Pg. Vall d'Hebron 119-129. 08024-Barcelona, Spain. Email: rafael.simo@vhir.org.

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Diabetes-induced pulmonary dysfunction is an emerging topic within the “new” complications of diabetes and in particular in type 2 diabetes (1). The lungs show a huge vascularization and are rich in proteins with an elevated turnover such as elastin and collagen, pointing this organ as a potential target to the harmful effects of chronic hyperglycaemia (1). In fact, an inverse association between metabolic control and spirometric values has been observed (2). In addition, positive changes in spirometric maneuvers after of 3-months of improvement in glycemic control has also been reported (3). The mechanisms to explain the cluster of pulmonary dysfunctions associated with type 2 diabetes are not yet fully understood. However, it has been argued that the most suitable explanations could be related with insulin resistance, nonenzymatic glycosylation of lung proteins, low-grade chronic inflammation state, microvascular damage, autonomic neuropathy and defects in the bronchiolar surfactant layer (1) (*Figure 1*). The manuscript of Kim *et al.* sheds light on this issue, exploring the connection between prediabetes, type 2 diabetes and pulmonary function in the *Korea National Health and Nutrition Examination Survey* (KNHANES) (4). Their data confirm not only that patients with type 2 diabetes exhibits lower values of forced expiratory volume in one second (FEV1)

and forced vital capacity (FVC) than control subjects, but also that the impaired pulmonary function also exists in the prediabetes stage. Overall, data from Kim *et al.* confirm previous information in Caucasian population and reinforce the notion that lung dysfunction is a progressive defect across glucose abnormalities, beginning in the prediabetes stage and expanding when type 2 diabetes appears (5). Notably, after adjustment for potential confounding factors (age, sex, body mass index, waist circumference and smoking status) an increase of 1% in the HbA1c level was associated with a -1.20% difference in FVC and a -0.77% difference in FEV1, with similar results when a 10 mg/dL increase in fasting plasma glucose was considered. As prevalence of prediabetes and undiagnosed diabetes are both increasing, a closer relationship between endocrinologists, pneumologists and primary care physicians is needed not only to better understand the deleterious effects of type 2 diabetes on lung parenchyma but to successfully target pulmonary dysfunction (6).

The potential advantageous role of physical activity on the respiratory muscles' strength and function has been reported in patients with lung diseases (7). Our group has also assessed the benefit from heart-healthy lifestyle behaviors on lung mechanics in a cross-sectional study

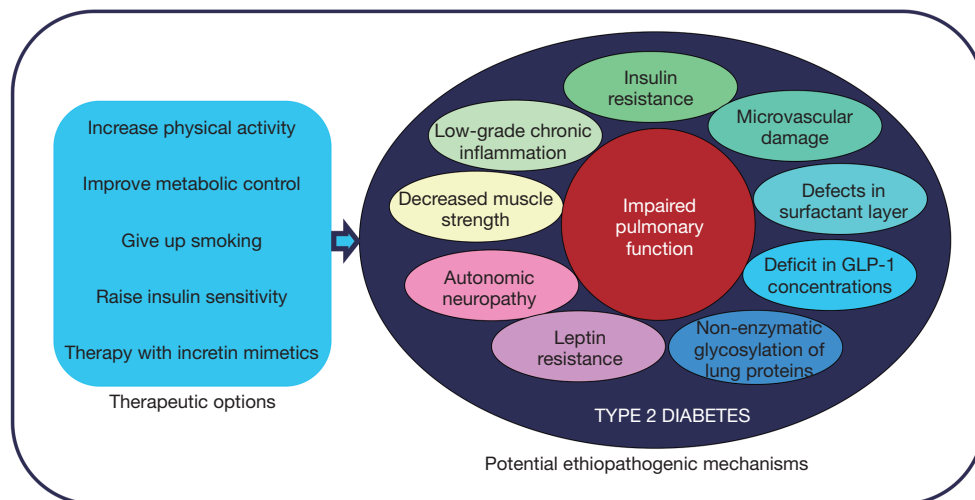


Figure 1 Suggested mechanisms to explain the involvement of pulmonary function and therapeutic options in patients with type 2 diabetes.

conducted in 3,020 Spanish middle-aged subjects free of lung disease (8). In this population, low physical activity was significant and independently associated with the presence of pulmonary impairment assessed by FEV1 <80% only in men (8). Kim *et al.* go one step further to explore the therapeutic implications of walking exercise in preventing a decreased pulmonary function in subjects with diabetes (4). Their results show that walking more than 300 minutes per week has a significant effect avoiding FVC and FEV1 decline. However, this beneficial effect disappeared after correction for smoking status, pointing to smoking cessation as a fundamental pillar among the strategies aimed at improving lung function of patients with diabetes.

Other possibilities that can be added to physical activity to treat or prevent lung dysfunction in patients with type 2 diabetes should be considered. The first option to consider would be the improvement of glycemic control. In this way, Gutiérrez-Carrasquilla *et al.* have recently communicated results from a prospective and interventional study to determine whether ameliorating metabolic control in patients with type 2 diabetes without known pulmonary disease during a three-month period produce significant changes in respiratory function (3). Therefore, in the *Sweet Breath Study* a favorable change in the spirometric parameters was just observed in the subgroup of participants who reached a reduction of their HbA1c higher than 0.5%, and this result was not related with weight reduction (3). More interesting, the spirometric parameters that appeared to be most sensitive to this rapid improvement of metabolic

control were peak expiratory flow (PEF) and FEV1, the former related with neuromuscular integrity. This relation between muscle strength and pulmonary function also reinforce the relevance to prescribe physical activity to patients with type 2 diabetes more vulnerable to develop lung involvement. And it is also another reason to insist on patients with diabetes about the need to achieve good glycemic control and thus prevent the development of late complications.

The glucagon like peptide 1 (GLP-1) receptor is expressed by alveolar type 2 cells, and its activation have been shown to stimulate the production of pulmonary surfactant in experimental studies (9). In fact, serum surfactant protein D (SP-D) has been proposed as a serum biomarker useful to identify patients with type 2 diabetes with defects in their bronchiolar surfactant layer (10). In this way, SP-D serum concentrations were inversely correlated with FEV1 and the stepwise multivariate regression analysis showed that a serum SP-D value equal or higher than 32.3 ng/mL was independently associated with a FEV1 <80% of predicted (10). Therefore, the underlying deficit of GLP-1 in type 2 diabetes could also be involved in the impairment of airway caliber. This hypothesis is now being tested in the LIRALUNG study (ClinicalTrials.gov Identifier: NCT02889510), a randomized double blind, crossover, placebo controlled clinical trial to evaluate the effect of liraglutide, a GLP-1 analogue, on lung function in patients with type 2 diabetes. On the other hand, worthy of additional attention is whether preventing the inactivation

of the endogenous GLP-1 through the pharmacological inhibition of the dipeptidyl peptidase-4 applies any effect on pulmonary function (1). On a similar level remains the possibility to enhance pulmonary function rising insulin sensitivity in patients with type 2 diabetes. Although there are no prospective studies addressing this option, a little retrospective study also in Korean patients showed how treatment with insulin sensitizers was independently associated with improvements in FVC compared with insulin therapy (11). And similarly, after adjustment for glycemic control and the known duration of type 2 diabetes, Colombian patients under treatment with metformine showed significantly lower differences from the expected values in FVC measures in comparison with patients receiving a secretagogue therapy (12).

To sum up, we hope that health professionals who take care of patients with type 2 diabetes begin to consider them as a vulnerable group for pulmonary dysfunction. Although clinical relevance of such changes has to date been little, we cannot forget that a 10% decrease in FEV1 is an independent predictor of all-cause mortality in type 2 diabetes (13). In this context, and while we find therapeutic targets capable of reversing this situation, investment in a healthy lifestyle that includes high physical activity, give up smoking and selected antidiabetic therapies to improve metabolic control should be recommended to patients with diabetes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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