Annals of Epidemiology xxx (2017) 1–7

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Low-grade systemic inflammation: a partial mediator of the relationship between diabetes and lung function

Jonathan Giovannelli MD [a,b,c,d,1], Philippe Trouiller [c,1], Sébastien Hulo MD, PhD [e,f], Natalie Chérot-Kornobis MD, PhD [e,f], Alina Ciuchete MD [a,d], Jean-Louis Edmé MD, PhD [e,f], Régis Matran MD, PhD [e,f], Philippe Amouyel MD, PhD [a,b,c,d], Aline Meirhaeghe PhD [a,d], Luc Dauchet MD, PhD [a,b,c,d,*]

[a] Univ. Lille, U1167 - RID-AGE - Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, F-59000 Lille, France
[b] Inserm, U1167, F-59000 Lille, France
[c] CHU Lille, Service d'épidémiologie, F-59000 Lille, France
[d] Institut Pasteur de Lille, F-59000 Lille, France
[e] University of Lille, Faculté de Médecine Henri Warembourg, Lille, France
[f] Lille University Hospital, Lille, France

ARTICLE INFO

Article history:
Received 8 February 2017
Accepted 13 November 2017
Available online xxx

Keywords:
Inflammation
C-reactive protein
Lung function
Diabetes complication
Mediation analysis

ABSTRACT

Purpose: An association has been consistently found between diabetes mellitus and decreased lung function. We evaluated to what extent low-grade inflammation (as measured by the level of high-sensitivity C-reactive protein [hs-CRP]) could explain this relationship.
Methods: A sample of 1878 middle-aged adults from the cross-sectional Enquête Littoral Souffle Air Biologie Environnement survey without self-reported pulmonary and atherosclerosis disease was included. A mediation analysis was performed to assess and quantify the hs-CRP level as a mediator of the relationship between diabetes and lung function.
Results: Diabetes was associated with higher hs-CRP level (+22.9%, 95% confidence interval = [5.1, 43.6]). The hs-CRP (>4 vs. ≤1 mg/L) was associated with lower percentage predicted values for the forced expiratory volume in the first second (FEV1) (−4% [−6.1, −1.9]) and forced vital capacity (FVC) (−4.4% [−6.5, −2.3]). Diabetes was associated with FEV1 (−3.5% [−5.8, −1.3]) and FVC (−3.6% [−5.9, −1.3]). The proportion of the effect that is mediated by hs-CRP was 12% [2.4, 37] and 13% [3.7, 39.4] for FEV1 and FVC, respectively.
Conclusions: Our results suggest that low-grade systemic inflammation could only explain a small part of the relationship between diabetes and lung function.

Introduction

Long-term complications of diabetes mellitus occurring on various organs, such as the kidneys, retina or nerves, are well established [1]. The degrading effect of diabetes on lung function, however, has been more recently suggested [2]. In a meta-analysis performed in 2010, diabetes was found to be associated with a modest impairment of lung function in a restrictive pattern [3].

Several potential pathophysiological mechanisms might explain this association: microangiopathy of the alveolar capillaries and pulmonary arterioles, chronic inflammation, autonomic neuropathy involving the respiratory muscles, loss of elastic recoil secondary to collagen glycosylation of lung parenchyma, hypoxia-induced insulin resistance, and low birth weight [4]. Low-grade inflammation is one of the most frequently cited potential mechanisms but, to the best of our knowledge, has not yet been characterized with regard to a putative association with lung damage.

One way to test this hypothesis is to study low-grade inflammation as a mediator in the relationship between diabetes and impaired lung function [5]. High-sensitivity C-reactive protein (hs-CRP) is widely used as a marker of low-grade systemic inflammation in clinical and epidemiological studies [6,7]. We therefore evaluated to what extent adjustment for low-grade

The authors declare that they have no conflicts of interest.

* Corresponding author. Epidemiology Unit, Lille University Hospital, 2 rue du Pr Laguesse, F-59037 Lille Cedex, France. Tel.: +33 320 445 518; fax: +33 320 446 945.
E-mail address: luc.dauchet@pasteur-lille.fr (L. Dauchet).

[1] Co-first authors: J.G. (as a PhD student) and P.T. (as a MD student) contributed equally to this work.

https://doi.org/10.1016/j.annepidem.2017.11.004
1047-2797/

systemic inflammation (as measured by the hs-CRP level) reduced the association between diabetes and lung function and therefore whether low-grade systemic inflammation mediated this association.

Methods

Participants

Methods of recruitment for the Enquête Littoral Souffle Air Biologie Environnement (ELISABET) cross-sectional survey (ClinicalTrials.gov identifier: NCT02490553) have been previously described [8]. In summary, male and female participants (aged from 40 to 64 years and living for at least 5 years in the same urban community) were selected from electoral rolls by random sampling, with stratification for gender, age, and center (Lille or Dunkirk, both in northern France) between 2011 and 2013. Each selected participant received a postal mail asking him to contact the coordinating team and make an appointment to carry out the data collection. In case of nonresponse, a telephone reminder was performed. Response rate was 32.5%. The study protocol was approved by the local institutional review board (CPP Nord Ouest IV, Lille, France; reference number: 2010-A00065-34), in compliance with the French legislation on biomedical research. All participants provided their written, informed consent to participation in the study.

Exclusion criteria

Participants of the ELISABET survey without acceptable spirometry data were excluded from this study, as were those with missing data for plasma glycemic markers or any of the covariates. To avoid confounding effects in the mediation analysis, we also excluded participants fulfilling at least one of the following three exclusion criteria: (1) a self-reported respiratory disease, (2) airway obstruction, as measured by spirometry testing, and (3) a self-reported atherosclerotic cardiovascular disease. Participants with values of hs-CRP above 10 mg/L were also excluded because they were assumed to suffer from acute illness or inflammation.

Diabetes definition

Diabetes mellitus was defined as ongoing diabetes treatment (oral medication or insulin) or a fasting blood glucose level greater than or equal to 1.26 g/L or a hemoglobin A1c value greater than or equal to 6.5%. We did not differentiate between type I and type II diabetes.

Spirometry testing

Spirometry testing was performed according to the 2005 American Thoracic Society/European Respiratory Society guidelines [9]. The spirometers (Micro 6000 spirometers [Medisoft, Sorinnes, Belgium]) were calibrated weekly. No bronchodilators were administered. For each participant, the spirometry test was repeated until three acceptable flow-volume loops were obtained. All spirometry data were validated by an experienced, specialist physician (J.L.E). Overall, 83% of the included participants had acceptable and reproducible spirometry. The % predicted values of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were calculated using the most recent equations from the Global Lung Initiative 2012 [10]. Airway obstruction was defined as a measured FEV1/FVC ratio below the lower limit of normal (fifth percentile) (Global Lung Initiative 2012), in the absence of bronchodilator reversibility testing.

High-sensitivity CRP

The hs-CRP was measured using nephelometric assay (BN ProSpec System, Siemens) in a sample of serum allowing a detection range of 0.17–10 mg/L. Values below the limit of detection were computed as $0.17/\sqrt{2}$ mg/L.

Covariates

The following variables were recorded: age, gender, educational level (number of years spent in full-time education, including primary school), height, body mass index (BMI), tobacco exposure, alcohol consumption, physical activity (low, moderate, or high; assessed using the International Physical Activity Questionnaire [11]), and serum creatinine. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula.

Statistical analyses

Association between diabetes and lung function

The first stage in the statistical analysis was to study the relationship between lung function and diabetes. To this end, the association between % predicted values of FEV1 or FVC (as the explained variables) and diabetes (as the explanatory variable) was modeled using multiple linear regression models with incremental adjustments (to evaluate the effect of the different confounders). The first model (model A) was adjusted for age, gender, height, and center. The second model (model B) was additionally adjusted for BMI. The third model (model C) was additionally adjusted for smoking status and tobacco consumption (pack-years). The fully adjusted model was additionally adjusted for educational level, hypertension, dyslipidemia, and alcohol consumption. A model additionally adjusted for physical activity and estimated glomerular filtration rate has been performed as a sensitivity analysis. Finally, interaction terms between diabetes and gender, BMI, and smoking were tested one at a time.

Mediation analysis

The second stage in the statistical analysis was a mediation analysis. We started by defining the mediation model within a four-step framework, as described by Baron and Kenny [5] and shown in Figure 1. Step 1 studied the relationship between diabetes and the hs-CRP level (path a). Step 2 studied the relationship between hs-CRP and FEV1 or FVC, while controlling for diabetes (path b). Step

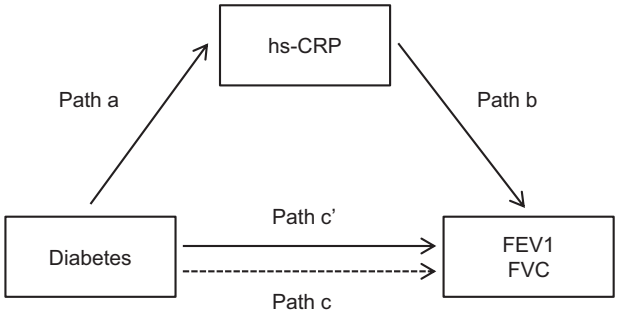

Fig. 1. Graphical representation of the mediation model. Path a probes the relationship between diabetes and the hs-CRP level. Path b probes the relationship between hs-CRP and FEV1 or FVC, while controlling for diabetes. Path c probes the relationship between diabetes and FEV1 or FVC. Path c' probes the relationship between diabetes and FEV1 or FVC, while controlling for the hs-CRP level. hs-CRP = high-sensitivity C-reactive protein; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity.