Potential enhanced association between obstructive lung disease and history of depression in patients with diabetes

Maria E Ramos-Nino¹,²,*, Charles D MacLean³, Benjamin Littenberg³
¹St. George’s University, Department of Microbiology, Immunology, and Pharmacology, Grenada, West Indies
²Department of Pathology and Laboratory Medicine, University of Vermont 05401, Burlington, Vermont, USA
³Department of Medicine, University of Vermont, Burlington, Vermont 05401, USA

Abstract

Background: Depression is one of the most common comorbidities of chronic diseases including diabetes and obstructive lung diseases (emphysema, chronic bronchitis, and asthma). Obstructive lung diseases and depression have few symptoms in common. However, they are both common in adults and associated with chronic inflammation. It is not clear if their coappearance in diabetic patients is coincidental or associated beyond that expected by chance.

Methods: A total of 1,003 adults with diabetes in community practice settings were interviewed at home at the time of their enrolment into the Vermont Diabetes Information System, a clinical decision support program. Patients self-reported their personal and clinical characteristics, including any obstructive lung disease. Laboratory data were obtained directly from the clinical laboratory, and current medications were obtained by direct observation of medication containers.
We performed a cross-sectional analysis of the interviewed subjects to assess a possible association between the prevalence of obstructive lung disease and depression.

Results: In a multivariate logistic regression model, obstructive lung disease was significantly associated with depression even after correcting for gender, obesity (≥30 kg/m²), high comorbidities (>2), low annual income (<$30,000/year), cigarette smoking, alcohol problems, and education level (odds ratio=1.83; 95% confidence interval 1.27, 2.62; P<0.01).
Conclusion: These data suggest a potential enhanced association between obstructive lung disease and depression in patients with diabetes. Future studies are needed to identify if inflammation is implicated in this association as a common denominator.

Keywords
Obstructive lung disease; Asthma; COPD; Depression; Diabetes

Background

Chronic diseases have increased in prevalence over the past decades in America [1,2]. Recent evidence suggests a link between inflammation and several chronic conditions including diabetes, cardiovascular disease, cancer, rheumatoid arthritis, inflammatory bowel disease, asthma, and chronic obstructive lung disease [3]. Together, chronic inflammatory diseases are the most significant cause of death worldwide [1].

Causes of systemic chronic inflammation include chronic infections, physical inactivity, obesity, intestinal dysbiosis, diet, psychological stress, exposure to xenobiotics such as tobacco smoking, and others [4]. The chronic inflammatory process activated by these triggers may lead to type 2 diabetes, steatohepatitis, cardiovascular disease, cancer, depression, autoimmune diseases, and neurodegenerative diseases (reviewed in [4]).

We aim to explore the association between two apparently independent chronic diseases, obstructive lung disease (asthma, and chronic obstructive pulmonary disease (COPD)) and depression, in a diabetic population. Symptoms of depression and anxiety have been reported before in individuals with obstructive lung disease as well as those with diabetes [5–9]. Depression and anxiety can impact quality of life and disease burden [6,10], as well as the development of complications and higher mortality rates [7,9,10]. Whether inflammation is the cause, or an effect of depression is not clear. Many studies have found elevated inflammatory cytokines and acute-phase proteins in patients with depression [11,12]. Chronic exposure to inflammation is thought to induce changes in neurotransmitters and neurocircuits that lead to depressive symptoms and that may interfere with treatment [11,13–15]. However, contradictory findings regarding the association between depression and inflammation can also be found in the literature [16].

Methods

This study is part of a larger project, the Vermont Diabetes Information System, a study of 7,412 adults with diabetes in primary care practices [17]. The subjects comprised all diabetic adults in 64 practices in Vermont and adjacent New York. A field survey was completed at study baseline with a subsample of subjects. Patients’ names were randomly sorted, and patients were contacted by telephone until a sample of approximately 15% of patients from each practice agreed to participate in the field survey to give a sample of 1,007 at the time of analysis. Four patients were dropped from the analysis due to incomplete information, leaving a final sample of 1,003.
Subjects completed a questionnaire at home and then were visited by a trained research assistant who reviewed the questionnaire responses, assisted the subject with any missing or unacceptable responses, reviewed the subject’s medications by direct examination of all medication containers, and measured their height and weight using a portable stadiometer and scale. Race, education, income, marital status, functional status, smoking, alcohol consumption, and comorbid conditions were obtained by questionnaire. To determine comorbidity, we used a modification of the Self-Administered Comorbidity Questionnaire [18] in which we asked each patient to indicate whether they had had the following conditions: heart attack, heart failure, peripheral arterial disease, stroke, dementia, rheumatic disease, peptic ulcer, cirrhosis, paralysis, renal insufficiency, diabetic vascular complications, AIDS/HIV, and depression. The primary outcome variable, presence of obstructive lung disease, was the patient’s response to the question “Do you have asthma, emphysema, or chronic bronchitis?” The primary predictor variable, history of depression, was determined by the patient’s responses to the following question: “Have you had depression?”

Most laboratory data were obtained from the patients’ local clinical laboratories, which all used the same Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications high performance, liquid chromatography (HPLC) method for the determination of glycosylated hemoglobin (A1C). Less than 1% of A1C tests were performed using the Bayer DCA 2000 immunoassay point of care instrument, which compares favorably with the HPLC method [19].

The research protocol was approved by the Committee on Human Research of the University of Vermont. The interviewed subjects provided written informed consent. The full study protocol and variables and the medication profiles of the subjects have been previously reported [17,20].

**Statistical approach**

We used logistic regression to assess the univariate relationship of obstructive lung disease as the outcome variable with history of depression as the predictor. We then adjusted for possible confounding by social and clinical factors. Potential confounders tested were gender (male/female), age (years), race (White/other), obesity (body mass index (BMI) \( \geq 30 \text{ kg/m}^2 \)), high comorbidities (>2 excluding diabetes, obstructive lung disease, and depression), glycosylated hemoglobin level (A1C; %), insulin use (yes/no), duration of diabetes in years, self-reported history of alcohol problems (yes/no), cigarette smoking (yes/no), low income (<$30,000 per year), and level of education (High School graduate or more). To reduce the number of variables in the final model, we excluded potential confounders that were associated with the outcome in univariate analyses with \( P > 0.15 \). Such a weak association implies that the variable is unlikely to be a confounder. We used Stata/SE v.16 (StataCorp, College Station, TX, USA) for all analyses.

**Results**

The general characteristics of the study population are described in Table 1. The study population was representative of adults with diabetes in primary care practices in northern
New England, USA. Because many of the subjects were over retirement age or suffered disabilities from chronic conditions, their income was lower than that of healthy younger Americans. The number of patients with obstructive lung disease in this population was 203 (20.2%). A total of 351 (35.0%) of the subjects had a history of depression (Table 1).

Table 2 presents univariate associations between obstructive lung disease and the other study variables that had the potential of being significantly associated with obstructive lung disease prevalence (Table 2).

Next, potential confounding variables associated with obstructive lung disease with P<0.15 were included in a logistic regression model using obstructive lung disease as the outcome (Table 3). This model showed a significant association between obstructive lung disease and depression (odds ratio (OR)=1.83; confidence interval (CI) (1.28-2.62); P<0.01).

Discussion

The prevalence of depression in diabetic patients is often higher than that in the general population, and depression accounts for a substantial part of the psychosocial burden of these disorders [21]. Although treatments can be effective, adjustments may be needed for patients with comorbidities. In addition, symptoms or treatments of comorbidities may interfere with the treatment of depression, and symptoms of depression may decrease adherence to treatment in these patients. Our data indicate that 20.2% of this cohort had chronic obstructive lung disease and 35% of the population had a history of depression. Furthermore, patients with chronic obstructive lung disease in this cohort had a higher prevalence of depression history (51.2%) compared to the population without obstructive lung disease (30.9%). These findings demonstrate a significant enhanced association between obstructive lung disease and depression in this diabetic cohort. Although it is unclear if depression causes lung disease or the reverse, we hypothesize that both are caused by a third factor: chronic inflammation, which is present in obstructive lung disease, diabetes, and depression [5-7,12]. Although social factors clearly play a role in these relationships, those we could measure were unlikely to explain the entire phenomenon.

One of the strengths of this study is that the interviewed subjects were a randomly selected subset of a large population of patients receiving care in New England, which makes them likely to be representative of other primary care patients in the US.

This study does, however, have several limitations, including self-report of obstructive lung disease, lack of confirmation of obstructive lung disease and depression diagnoses, inability to distinguish between asthma and COPD patients, and lack of information on the time relation between the onset of obstructive lung disease and the onset of depression. As in any cross-sectional study, unmeasured confounders could be responsible for the apparent associations found.

Conclusion

Our findings suggest that the presence of obstructive lung disease may enhance depression in patients with diabetes. The diagnosis of depression in diabetic patients with obstructive
lung diseases is important as it may be related to disease control and prognosis. Further research is needed to identify the mechanisms involved.

Funding

This research was supported by NIH grants RO1 DK61167, K24 DK068380 (BL).

Availability of Data and Materials

All data analyzed during this study are included in this published article.

Abbreviations:

VDIS Vermont Diabetes Information System  
BMI Body Mass Index  
COPD Chronic Obstructive Pulmonary Disease  
A1C Glycosylated hemoglobin  
CI Confidence Interval  
SD Standard Deviation  
N Number of subjects with the characteristic  
OR Odds Ratio

References

1. Centers for Disease control and Prevention. Chronic Diseases in America. Available from: https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm Accessed on: 24 March 2021.
2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov 10;392(10159):1736–88.
3. Zhong J, Shi G. Regulation of inflammation in chronic disease. Frontiers in Immunology. 2019 Apr 12;10:737. [PubMed: 31031750]
4. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nature Medicine. 2019 Dec;25(12):1822–32.
5. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabetic Medicine. 2006 Nov;23(11):1165–73. [PubMed: 17054590]
6. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. General Hospital Psychiatry. 2007 Mar 1;29(2):147–55. [PubMed: 17366664]
7. Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. International Journal of Geriatric Psychiatry. 2010 Dec;25(12):1209–21. [PubMed: 20033905]
8. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. European Respiratory Review. 2014 Sep 1;23(133):345–9. [PubMed: 25176970]
9. Stoop CH, Nefs G, Pommer AM, Pop VJ, Pouwer F. Effectiveness of a stepped care intervention for anxiety and depression in people with diabetes, asthma or COPD in primary care: a randomized controlled trial. Journal of Affective Disorders. 2015 Sep 15;184:269–76. [PubMed: 26118755]

10. Lavoie KL, Bacon SL, Barone S, Cartier A, Ditto B, Labrecque M. What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both?. Chest. 2006 Oct 1;130(4):1039–47. [PubMed: 17035436]

11. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013 Aug 29;246:199–229. [PubMed: 23644052]

12. Berk M, Williams LJ, Jacka FN, O’Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from?. BMC Medicine. 2013 Dec;11(1):1–6. [PubMed: 23281898]

13. Felger JC. Role of Inflammation in Depression and Treatment Implications. Handb Exp Pharmacol. 2019;250:255–286. [PubMed: 30368652]

14. Felger JC. Imaging the role of inflammation in mood and anxiety-related disorders. Current Neuropharmacology. 2018 Jun 1;16(5):533–58. [PubMed: 29173175]

15. Adzic M, Brkic Z, Mitic M, Francija E, Jovicic MJ, Radulovic J, et al. Therapeutic strategies for treatment of inflammation-related depression. Current Neuropharmacology. 2018 Feb 1;16(2):176–209. [PubMed: 28847294]

16. Raison CL, Miller AH. Is depression an inflammatory disorder?. Current Psychiatry Reports. 2011 Dec 1;13(6):467–75. [PubMed: 21927805]

17. MacLean CD, Littenberg B, Gagnon M, Reardon M, Turner PD, Jordan CY. The Vermont Diabetes Information System (VDIS): study design and subject recruitment for a cluster randomized trial of a decision support system in a regional sample of primary care practices. Clinical Trials. 2004 Dec;1(6):532–44. [PubMed: 16279294]

18. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2003 Apr 15;49(2):156–63.

19. Tamborlane WV, Kollman C, Steffes MW, Ruedy KI, Dongyuan X, Beck RW, et al. Comparison of fingerstick hemoglobin A1c levels assayed by DCA 2000 with the DCCT/EDIC central laboratory assay: results of a Diabetes Research in Children Network (DirecNet) Study. Pediatr Diabetes. 2005 Mar;6(1):13–6. [PubMed: 15787896]

20. MacLean CD, Littenberg B, Kennedy AG. Limitations of diabetes pharmacotherapy: Results from the Vermont Diabetes Information System study. BMC Family Practice. 2006 Dec;7(1):1–6. [PubMed: 16396688]

21. Holt RI, de Groot M, Golden SH. Diabetes and depression. Curr Diab Rep. 2014 Jun;14(6):491. [PubMed: 24743941]
Table 1:
Baseline characteristics of 1,003 adults with diabetes.

| Characteristic                              | N (%) or mean (sd) |
|---------------------------------------------|--------------------|
| Age, years                                  | 64.8 (12.0)        |
| Gender: Men                                 | 457 (45.6%)        |
| Gender: Women                               | 546 (54.4%)        |
| White race                                  | 973 (97.3%)        |
| Median income ($/year)                      | 15,000-29,999      |
| Low annual income (<$30,000)                | 548 (59.1%)        |
| Level of education (High School graduate or higher) | 762 (75.7%)      |
| Body mass index (BMI) kg/m$^2$               | 33.8 (7.4)         |
| Obese (BMI > 30 kg/m$^2$)                   | 666 (67.3%)        |
| Glycosylated hemoglobin A1C %               | 7.1 (1.3)          |
| Insulin use                                 | 186 (18.5%)        |
| Duration of diabetes, years                 | 10.2 (10.3)        |
| Obstructive lung disease prevalence         | 203 (20.2%)        |
| Depression                                  | 351 (35.0%)        |
| High number of comorbidities (>2)           | 613 (60.9%)        |
| Alcohol problem                             | 78 (7.9%)          |
| Cigarette smoking                           | 170 (17.0%)        |

sd: standard deviation; n: number of subjects with the characteristic.
Table 2:

Univariate associations between obstructive lung disease and other patient characteristics.

| Characteristic              | Obstructive lung disease patients | Non-obstructive lung disease patients | OR   | P    |
|-----------------------------|-----------------------------------|---------------------------------------|------|------|
| Number of subjects          | 203                               | 800                                   |      |      |
| Depression                  | 51.2%                             | 30.9%                                 | 2.35 | <0.01|
| Age, years                  | 64.3 (11.4)                       | 64.9 (12.1)                           | 1.00 | 0.54 |
| Male                        | 33.5%                             | 48.6%                                 | 0.53 | <0.01|
| White race                  | 96.1%                             | 97.6%                                 | 0.60 | 0.23 |
| Low annual income           | 75.7%                             | 54.8%                                 | 2.57 | <0.01|
| High School graduate        | 64.5%                             | 78.4%                                 | 0.50 | <0.01|
| Obese (BMI>30 kg/m²)        | 77.0%                             | 64.8%                                 | 1.82 | <0.01|
| A1C, mg %                   | 7.2 (1.3)                         | 7.1 (1.3)                             | 1.03 | 0.67 |
| Insulin use                 | 27.2%                             | 22.8%                                 | 1.27 | 0.20 |
| Duration of diabetes, years | 11.1 (10.6)                       | 10.0 (10.3)                           | 1.01 | 0.20 |
| High comorbidities (>2)     | 73.4%                             | 57.5%                                 | 2.04 | <0.01|
| Alcohol problem             | 12.1%                             | 6.8%                                  | 1.88 | 0.02 |
| Cigarette smoking           | 24.3%                             | 15.1%                                 | 1.79 | <0.01|

Each cell contains either % or mean (standard deviation).
Table 3:
Multivariate logistic regression: obstructive lung disease vs. depression and potential confounders (N=903)

| Characteristic         | OR  | P      | 95% CI   |
|------------------------|-----|--------|----------|
| Depression             | 1.83| <0.01  | 1.28, 2.62 |
| Gender (male)          | 0.52| <0.01  | 0.36, 0.75 |
| Low annual income      | 1.78| 0.01   | 1.18, 2.69 |
| High School graduate   | 0.58| 0.01   | 0.40, 0.86 |
| Obesity                | 1.63| 0.02   | 1.09, 2.44 |
| High comorbidities     | 1.77| <0.01  | 1.21, 2.58 |
| Alcohol problem        | 1.56| 0.13   | 0.88, 2.77 |
| Cigarette smoking      | 1.43| 0.10   | 0.93, 2.18 |