Original Article

Relationship between pulmonary function and elevated glycated hemoglobin levels in health checkups: A cross-sectional observational study in Japanese participants

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ABSTRACT

Background: Insulin resistance has been associated with cytokines, including interleukin-6 and tumor necrosis factor alpha soluble receptor, both of which are elevated in chronic obstructive pulmonary disease (COPD). Few studies have investigated the relationship between pulmonary function tests using spirometry (PFT) and fasting plasma glucose (FPG) or glycated hemoglobin (HbA1c) levels in Japanese participants. The purpose of this study was to clarify the relationship between PFT in Japanese people who had health checkups and their FPG or HbA1c levels. In the context of preventative medicine, we intend to connect early detection of COPD to an index of blood sugar.

Methods: From August 2013 through March 2014, 1019 participants underwent health checkups. PFT, FPG, and HbA1c measurements were conducted. HbA1c levels were measured according to National Glycohemoglobin Standardization Program guidelines.

Results: Participants with FPG ≥100 mg/dL and HbA1c ≥5.6% showed a significantly lower forced expiratory volume in 1 s:forced vital capacity ratio (FEV1/FVC) compared to participants with lower FPG and HbA1c levels. Prevalence of FEV1/FVC values <70% in PFT differed significantly depending on sex, age, body mass index, FPG, HbA1c, and smoking habits. Age ≥60 years, HbA1c ≥5.6%, and current or former smoking were associated with FEV1/FVC values <70%.

Conclusion: In Japan, HbA1c levels were higher in participants with FEV1/FVC <70% in PFT than in those with FEV1/FVC ≥70%. In preventive medicine, PFT by spirometry should be performed in elderly participants with elevated HbA1c levels who are current or former smokers.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory lung disease caused by long-term smoking. Globally, COPD is the fourth-leading cause of death, and in Japan, there is a tendency of high under-diagnosis of patients with COPD.1,2 COPD progression leads to inflammation, which is potentially lethal. The main symptoms of COPD are dyspnea and breathlessness during activities. Progression of COPD also has a significant impact on the patient quality of life (QOL). Therefore, early detection and implementation of a suitable treatment for COPD is paramount.

On the other hand, COPD is a systemic inflammatory disease that has been associated with various comorbidities, such as diabetes mellitus (DM), hyperlipidemia (HL), hypertension (HT), and cardiovascular disease.3−5 DM is a lifestyle-related disease associated with poor diet, such as consumption of high-fat meals, or a lack of exercise, which often manifests as a metabolic syndrome; COPD has been closely linked to smoking history and is considered a major risk factor for DM.6,7

Interestingly, smoking has also been related to the development of insulin resistance.8−10 Additionally, cytokines, such as interleukin-6 and tumor necrosis factor alpha soluble receptor, which are elevated in COPD, have been associated with the development of insulin resistance in liver and muscle
tissues; as a result, COPD has been postulated as a risk factor for DM.11–14

A previous study involving 47 million people in a National Hospital Survey investigated the prevalence of comorbidities in patients with COPD and found that the prevalence of DM in patients with COPD was significantly higher than that in patients without COPD.15 In addition, a recent large-scale cohort study suggested that COPD was associated with an increased risk of DM, myocardial infarction, and heart failure.11,16 Therefore, it is necessary to consider DM management in the treatment of patients with COPD because DM is an important prognosticator in patients with COPD.17 A recent meta-analysis indicated that pulmonary function is compromised in patients with DM and pre-diabetes compared to participants with normal fasting plasma glucose (FPG) levels.18,19 However, the association between COPD and DM has not yet been elucidated, and few studies have investigated the relationships of pulmonary function tests in people with undiagnosed COPD with FPG or glycated hemoglobin (HbA1c) levels.

In Japan, to detect lifestyle-related diseases at an early stage, regular health checkups are recommended for adults aged ≥40 years. The purpose of this study was to clarify the relationships of pulmonary function tests using spirometry (PFT) in people with undiagnosed COPD who had health checkups in Japan with their FPG or HbA1c from the perspective of preventive medicine.

Methods

In this cross-sectional observational study, participants were selected at the Japan Community Health care Organization (JCHO) Saga Health Administration Center, in Saga Prefecture, Japan. This center provides care for the prevention and early detection of lifestyle-related diseases. Eligible participants included adults aged ≥40 years who attended the center for health checkups from August 2013 through March 2014. Of the 1091 participants enrolled, 72 were excluded because they had physician-diagnosed asthma (n = 52), bronchiectasis (n = 16), or displayed a restrictive abnormality on spirometry (n = 4). Ultimately, we studied 1019 participants. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board of JCHO Saga Central Hospital and was conducted according to the principles set out in the Helsinki Declaration.

Pulmonary function tests

Pulmonary function tests, including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), percent predicted FEV1 (% FEV1), and the FEV1:FVC ratio were measured using conventional spirometry (Chestgraph HI-701; Chest Co., Tokyo, Japan), as recommended by the American Thoracic Society.20 According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),21 the FEV1/FVC is 70–80% in normal adults, and a value <70% indicates airflow limitation and the possibility of COPD. In adults with an FEV1/FVC <70%, GOLD stage I reflects a mild airflow limitation (% FEV1 [predicted] ≥80%), stage II is moderate (FEV1 ≤50%; %FEV1 <80%), stage III is severe (FEV1 ≤30%; %FEV1 <50%), stage IV is very severe (%FEV1 <30% or <50% in conjunction with chronic respiratory failure).21 We adopted this GOLD classification in the present study.

Data for health checkups

Blood samples were obtained for biochemical assays, including FPG and HbA1c, assays, which were measured using methods suggested by the National Glycohemoglobin Standardization Program guidelines. FPG levels ≥100 mg/dL or HbA1c levels ≥5.6% indicate pre-diabetes and an increased risk of developing type 2 DM.22,23 In this study, we defined participants as having a “high glucose level” if they met either of these criteria. All participants filled out a standard questionnaire on smoking history (Never, non-smoker; Current, current smoker; or Former, past smoker), patterns of physical activity, and a detailed medical history, including any regular medications. Smoking was defined as a dichotomous variable with the answer ‘yes’ to the question ‘Have you smoked at least 100 cigarettes in your entire life?’ This classification combines former and current smokers (with non-smokers as the reference group), and is in line with the definition of smoking status adopted by the United States Centers for Disease Control and Prevention (CDC).24

Analysis

Relationships among sex, age, body mass index (BMI), FPG levels, HbA1c levels, and the presence or absence of DM, HL, HT, and FEV1/FVC <70% or FEV1/FVC ≥70% were examined using the chi-square (χ²) test. Logistic regression analysis was then conducted to identify risk predictors that resulted in an FEV1/FVC <70%. The final multivariate model included variables that were retained in a backward analysis, with p < 0.05 indicating statistical significance. All statistical analyses were performed using SPSS version 22.0 (SPSS Japan Inc., Tokyo, Japan).

Results

A total of 1019 participants’ demographics are presented in Table 1. Of the 95 participants with FEV1/FVC <70%, 7 (7.4%) had comorbid type 2 DM.

Participants with high glucose levels (FPG ≥100 mg/dL) had a significantly reduced FEV1:FVC ratio (p = 0.009) (Fig. 1). In addition,
participants with high HbA1c levels (≥5.6%) had significantly reduced FEV1/FVC (p < 0.0001) (Fig. 2).

Prevalence of FEV1/FVC < 70% differed significantly according to sex, age, BMI, FPG, HbA1c, and smoking status, whereas there was no relationship between the prevalence of FEV1/FVC < 70% and DM, HL, or HT (Table 2).

Multivariable logistic regression was performed to estimate the risk of FEV1/FVC < 70% associated with potential predictors, including clinical variables, such as sex, age, BMI, FPG, HbA1c, and smoking status. As a result, logistic regression analysis revealed that age (≥60 years), HbA1c levels (≥5.6%), current smoking, and former smoking were significantly associated with a FEV1/FVC < 70% (Table 3).

![Fig. 1. Relationship between fasting plasma glucose level and pulmonary function. The bar graph represents the mean value and the horizontal axis represents the standard deviations of forced expiratory volume in 1 s:forced vital capacity ratios (FEV1/FVC). Participants with fasting plasma glucose (FPG) levels of ≥100 mg/dL had significantly lower FEV1/FVC compared to those with FPG levels of <100 mg/dL (p = 0.009, Welch T-test).](S. Baba et al. / Journal of Epidemiology 27 (2017) 511–515)

![Fig. 2. Relationship between glycated hemoglobin level and pulmonary function. The bar graph represents the mean value and the horizontal axis represents the standard deviations of forced expiratory volume in 1 s:forced vital capacity ratios (FEV1/FVC). Participants with glycated hemoglobin levels (HbA1c) of ≥5.6% had significantly lower FEV1/FVC compared to those with HbA1c levels of <5.6% (p < 0.0001, Welch T-test).](S. Baba et al. / Journal of Epidemiology 27 (2017) 511–515)

**Table 2**

| Factor                  | FEV1/FVC < 70% (n = 95) | FEV1/FVC ≥ 70% (n = 924) | P value |
|-------------------------|-------------------------|--------------------------|---------|
| Sex, n                  |                         |                          |         |
| Male/Female             | 74/21                   | 621/303                  | 0.033   |
| Age, n                  |                         |                          |         |
| <60 years/≥60 years     | 59/36                   | 815/109                  | <0.001  |
| Body mass index, n      |                         |                          |         |
| <25 kg/m²/≥25 kg/m²     | 79/16                   | 681/241                  | 0.048   |
| FPG, n                  |                         |                          |         |
| <100 mg/dL/≥100 mg/dL   | 66/29                   | 746/176                  | 0.008   |
| HbA1c, n                |                         |                          |         |
| <5.6%/≥5.6%             | 34/61                   | 554/370                  | 0.004   |
| Smoking status, n       |                         |                          |         |
| Never/Current           | 25/35                   | 401/234                  | 0.001   |
| Never/Former            | 25/35                   | 401/289                  | 0.014   |
| Former/Current          | 35/25                   | 289/234                  | 0.407   |
| Disease                 |                         |                          |         |
| DM Yes/No               | 7/88                    | 47/877                   | 0.344   |
| HT Yes/No               | 12/83                   | 89/835                   | 0.221   |
| CVD Yes/No              | 17/78                   | 127/797                  | 0.170   |

CVD, cardiovascular disease; DM, diabetes mellitus; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HL, hyperlipidemia; HT, hypertension.

**Table 3**

| Factors                  | Odds ratio | 95% CI | P value |
|--------------------------|------------|--------|---------|
| Age, years               |            |        |         |
| <60 years/≥60 years      | Reference  | 3.20   | 1.82–5.63 | 0.000 |
| Body mass index, kg/m²   |            |        |         |
| <25/≥25                  | Reference  | 0.27   | 0.13–0.59 | 0.001 |
| HbA1c, %                 |            |        |         |
| <5.6%/≥5.6%              | Reference  | 2.04   | 1.23–3.40 | 0.006 |
| Smoking status           |            |        |         |
| Former/Current           | 1.98       | 1.07–3.67 | 0.031 |
| Current                  | 3.24       | 1.71–6.15 | <0.001 |

CI, confidence interval; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; HbA1c, glycated hemoglobin.

**Discussion**

In the present study, participants with high glucose levels (FPG ≥100 mg/dL or HbA1c ≥5.6%) had significantly lower FEV1/FVC ratios compared to those who did not. In addition, sex, age, BMI, FPG levels, HbA1c levels, and smoking history were all associated with FEV1/FVC < 70%. In particular, people with FEV1/FVC values <70% had significantly elevated HbA1c levels.

Generally, an FEV1/FVC ratio less than 70% on spirometry will result in a diagnosis of COPD. Of the 95 participants with an FEV1/FVC < 70%, 61 participants showed a HbA1c of more than 5.6% and all had GOLD stage I-II defects (mild-moderate). Only 7.4% of patients with COPD had comorbid DM, which was lower than the 16.3% reported by Schnell et al. However, the findings of Schnell et al were determined using data from the large-scale NHANES.
study, which was conducted in the United States and comprised a population of 10 million COPD sufferers. The discrepancy between our study and theirs could be because of significant population differences between Japan and the United States.

A previous meta-analysis suggested an association between COPD and DM,\(^{18}\) and it has been reported that pulmonary function is significantly lower in patients with COPD who have comorbidities, such as DM, HL, and HT, than in COPD patients who do not have comorbidities.\(^{26,27}\) Despite this, the present study did not show any significant associations of the prevalence of COPD with these comorbidities. This was surprising because previous studies have indicated that the prevalence of DM and COPD comorbidity in patients with high glucose (as indicated by elevated FPG and HbA1c) was \(>10\%\) and that these patients had significantly reduced pulmonary function.\(^{28–30}\)

Based on these results, it was thought that participants who were elderly (\(\geq 60\) years), had high HbA1c levels, and were current smokers had high tendency to toward impaired pulmonary function. Furthermore, in the present study, the risk of having a FEV1/FVC <70% in participants with high HbA1c levels was approximately double that in those with lower HbA1c levels. The present study revealed that FEV1/FVC <70% was associated with HbA1c but not for FPG. FPG was determined from blood samples; however, it only indicates the plasma glucose level at that point in time. In contrast, HbA1c provides data reflecting the mean plasma glucose control level over the past 1–3 months. Therefore, it is thought that HbA1c is a better marker as an index of glycemic control. Therefore, from the perspective of preventive medicine, PFT should be conducted when participants undergoing health checkups have elevated FPG or HbA1c levels.

In this study, we stratified the data according to sex in the statistical analysis; however, we were not able to find a sex-related association. It is known that COPD is more common in men; however, in the older populations, the proportion of women is greater because of the high smoking rate among women in Japan.\(^{31}\) If we investigate the number of cigarettes smoked (number of packs per year) according to sex in this study, it is likely that there may have been an association between the two. Future studies should investigate the number of cigarettes smoked to determine this.

Our study has several limitations. First, only a small proportion of patients had DM in our study sample. Findings from the 2007 National Health and Nutrition Survey in Japan showed that 15.3% of people were “strongly suspected of having diabetes” as defined using a HbA1c level \(\geq 6.1\%\) or self-reporting of pharmacotherapeutic intake for diabetes.\(^{32}\) In our study, the percentage of diabetics with HbA1c levels \(\geq 6.1\%\) was 6.7%, which is low. Many participants showed good glycemic control. Furthermore, a larger sample should be enrolled, and prospective follow-up of participants is necessary. Second, our participants had lower FVC and FEV1 values than the general population in Japan.\(^{33,34}\) This explains the slightly lower FEV1/FVC ratios compared to previous studies. As this study was conducted at a fixed point in time, pre-COPD participants might also be included. Although our result reflects the general tendency of the study participants, there is a limit to grasping the general trend of FEV1/FVC values of <70%. Further mechanistic studies are needed to evaluate the relationship between FEV1/FVC <70% and glycemic control.

In conclusion, participants with FEV1/FVC <70% had significantly elevated HbA1c levels compared to those with FEV1/FVC \(\geq 70\%\). This suggests that, in Japan, people with undiagnosed COPD who have elevated HbA1c levels should undergo spirometry to evaluate pulmonary function for early detection of COPD. In particular, participants aged \(\geq 60\) years with elevated HbA1c who are smokers or former smokers should undergo screening for COPD. Early detection of COPD may lead to improved management and reduce medical expenditures.

**Conflicts of interest**

None declared.

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**References**

1. Aizawa H. Epidemiology of COPD in Japan: NICE study (Nippon COPD Epidemiology Study). Nihon Rinsho. 2007;65:599–604 [In Japanese].
2. Minakata Y, Ichinose M. Epidemiology of COPD in Japan. Nihon Rinsho. 2011;69:1721–1726 [In Japanese].
3. Parappil A, Depczynski B, Collett P, Marks GB. Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. Respir Med. 2010;15:918–922.
4. Barnes PJ. Chronic obstructive pulmonary disease: effects beyond the lungs. PLoS Med. 2010;7:e1000220.
5. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of ‘overspill’ of inflammatory mediators from the lungs? Review of the evidence. Thorax. 2010;65:930–936.
6. Sinden NJ, Stockley RA. Chronic obstructive pulmonary disease: an update of treatment related to frequently associated comorbidities. Ther Adv Chronic Dis. 2010;1:43–57.
7. Koskela J, Kilpeläinen M, Kupiainen H, et al. Co-morbidities are the key nom- inators of the health related quality of life in mild and moderate COPD. BMC Pulm Med. 2014;14:102.
8. Eliaison R, Artwell S, Taskinen M, Smith U. The Insulin resistance syndrome in smokers is related to smoking habits. Arterioscler Thromb. 1994;14:1946–1950.
9. Bergman BC, Perreault L, Humerdosse D, et al. Novel and reversible mechanism of smoking-induced insulin resistance in humans. Diabetes. 2012;61:3156–3166.
10. Ohkuma T, Iwase M, Fuji H, et al. Dose- and time-dependent association of smoking and its cessation with glycemic control and insulin resistance in male patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry. PLoS One. 2015;10:e012203.
11. Bolton CE, Evans M, Ionescu AA, et al. Insulin resistance and inflammation – a further systematic comparison of COPD. COPD. 2007;4:121–126.
12. Urban MH, Ay L, Funk GC, et al. Insulin resistance may contribute to vascular dysfunction in patients with chronic obstructive pulmonary disease. Wien Klin Wochenschr. 2014;126:106–112.
13. Eker S, Ayaz L, Tamer L, Ulubas B. Leptin, visfan, insulin resistance, and body composition change in chronic obstructive pulmonary disease. Scand J Clin Lab Invest. 2010;70:40–44.
14. Minas M, Kostikas K, Papatsoannou AI, et al. The association of metabolic syn- drome with adipose tissue hormones and insulin resistance in patients with COPD without co-morbidities. COPD. 2011;8:414–420.
15. Holguin F, Coleh E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest. 2005;128:2005–2011.
16. Thomsen M, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory bio- markers and comorbidities in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186:982–988.
17. Marts S, Muñoz X, Rios J, Morell F, Ferrer J. Body weight and comorbidity predict mortality in COPD patients treated with oxygen therapy. Eur Respir J. 2006;4:689–696.
18. van den Boor T, Giskjer HR, Zeegers MP, Schols AM. Pulmonary function in diabetes a metaanalysis. A metaanalysis. Nihon Rinsho. 2005;63:420.
19. Yamane T, Yokoyama A, Kitahara Y, et al. Cross-sectional and prospective study of the association between lung function and prediabetes. BMJ Open. 2013;3: e002179.
20. Standardization of spirometry. 1994 update. American thoracic society. Am J Respir Crit Care Med. 1995;152:1107–1136.
21. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176:532–555.

22. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care. 2015;38:S8–S16.

23. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig. 2010;1:212–228.

24. Centers for Disease Control and Prevention. Health topic data guide: smoking status. Available at: http://dhds.cdc.gov/guides/healthtopics/indicator?i=smokingstatus. Accessed 16 July 2016.

25. Schnell K, Weiss CO, Lee T, et al. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008. BMC Pulm Med. 2012;12:26.

26. Barr RG, Celli BR, Mannino DM, et al. Comorbidities, patient knowledge, and disease management in a national sample of patients with chronic obstructive pulmonary disease. Am J Med. 2009;122:348–355.

27. Makarevich AE, Valevich VE, Pochtavtsev AU. Evaluation of pulmonary hypertension in COPD patients with diabetes. Adv Med Sci. 2007;52:265–272.

28. Dennis RJ, Maldonado D, Rojas MX, et al. Inadequate glucose control in type 2 diabetes is associated with impaired lung function and systemic inflammation: a cross-sectional study. BMC Pulm Med. 2010;10:38.

29. Walter RE, Beiser A, Givelber RJ, O’Connor GT, Gottlieb DJ. Association between glycemic state and lung function. Am J Respir Crit Care Med. 2003;167:911–916.

30. Luijks HD, de Grauw WJ, Bor JH, et al. Exploring the impact of chronic obstructive pulmonary disease (COPD) on diabetes control in diabetes patients: a prospective observational study in general practice. NPJ Prim Care Respir Med. 2015;25:15032.

31. Suzuki S, Kojima M, Tokudome S, et al. Obesity/weight gain and breast cancer risk: findings from the Japan collaborative cohort study for the evaluation of cancer risk. J Epidemiol. 2013;23:139–145.

32. Morimoto A, Nishimura R, Tajima N. Trends in the epidemiology of patients with diabetes in Japan. Jpn Med Assoc J. 2010;53:36–40.

33. Kitahara Y, Hattori N, Yokoyama A, et al. The influence of lung function on exercise capacity in patients with type 2 diabetes. Hiroshima J Med Sci. 2010;59:7–13.

34. Heianza Y, Arase Y, Tsuji H, et al. Low lung function and risk of type 2 diabetes in Japanese men: the toranomon hospital health management center study 9 (TOPICS 9). Mayo Clin Proc. 2012;87:853–861.