Cross-sectional and prospective study of the association between lung function and prediabetes

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ABSTRACT

Objectives: A growing body of evidence suggests that there is a relationship between impaired lung function and the risk of developing diabetes mellitus (DM). However, it is not known if this reflects a causal effect of lung function on glucose metabolism. To clarify the relationship between lung function and the development of DM, we examined the incidence of newly diagnosed prediabetes (a precursor of DM) among subjects with normal glucose tolerance (NGT) at baseline.

Design: Primary analysis of an occupational cohort with both cross-sectional and longitudinal data (follow-up duration mean±SD: 28.4±6.1 months).

Setting and participants: Data were analysed from 1058 men in a cross-sectional study and from 560 men with NGT in a longitudinal study.

Outcomes and methods: Impaired lung function (per cent predicted value of forced vital capacity (%FVC) or per cent value of forced expiratory volume 1 s/FVC (FEV1/FVC ratio)) in relation to the ratio of prediabetes or DM in a cross-sectional study and development of new prediabetes in a longitudinal study. NGT, prediabetes including impaired glucose tolerance (IGT) and increased fasting glucose (IFG) and DM were diagnosed according to the American Diabetes Association criteria for a particular type of prediabetes, impaired glucose tolerance rather than impaired fasting glucose.

Measurements and main results: %FVC at baseline, but not FEV1/FVC ratio at baseline, was significantly associated with the incidences of DM and prediabetes. Among prediabetes, IGT but not IFG was associated with %FVC. During follow-up, 102 subjects developed prediabetes among those with NGT. A low %FVC, but not FEV1/FVC ratio, was predictive of an increased risk for development of IGT, but not of IFG.

Conclusions: Low lung volume is associated with an increased risk for the development of prediabetes, especially IGT, in Japanese men. Although there is published evidence for an association between chronic obstructive pulmonary disease and DM, prediabetes is not associated with the early stage of COPD.

ARTICLE SUMMARY

Article focus
- We hypothesised that lung function is associated with the development of impaired glucose metabolism. To investigate this, the data of an occupational cohort were analysed from 1058 men in a cross-sectional study and from 560 men with normal glucose tolerance (NGT) in a longitudinal study.

Key messages
- Low lung volume was significantly associated with the incidence of prediabetes or diabetes mellitus (DM) in both cross-sectional and longitudinal studies.
- Low lung volume is an independent risk factor for a particular type of prediabetes, impaired glucose tolerance rather than impaired fasting glucose. Our results suggested that prediabetes is not associated with the early stage of COPD, although there are published evidences for an association between COPD and DM.

Strengths and limitations of this study
- This is the first study that prospectively examined the incidence of newly diagnosed prediabetes among subjects with NGT at baseline. There are several limitations including that the subjects were limited to Japanese men and our occupational cohort may possibly be healthier than the general population.

INTRODUCTION

Accumulating evidence suggests that there is a close relationship between impaired lung function and diabetes mellitus (DM). Population-based studies have demonstrated associations between both obstructive and restrictive lung impairment and insulin resistance or DM.1–9 A representative obstructive lung disease, chronic obstructive pulmonary disease (COPD), is now well known to be associated with a variety of comorbidities, including DM.10–13 However, an accelerated decline of lung function has been observed in patients with DM.14 The incidence rates of COPD, asthma, lung fibrosis and pneumonia

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are greater in patients with DM than in those without DM. The incidence of death from COPD is also increased in DM.

The metabolic stage between normal glucose homeostasis and DM is called prediabetes, which the WHO divides into impaired glucose tolerance (IGT) and increased fasting glucose (IFG). Both IFG and IGT are the established risk factors for DM. Subjects with prediabetes also have higher incidence rates of microvascular complications, including neuropathy, retinopathy and nephropathy, than do those with normal glucose tolerance (NGT).

We reported previously that smokers with airflow limitation had subclinical atherosclerosis as evidenced by carotid intima-media thickness (CIMT). Although we excluded subjects with DM, the prediabetic state may influence the association, since prediabetes per se was accompanied by a modest but significant increase in the risk for developing CVD, as described above. However, there is no information regarding the association between lung function and prediabetes. Therefore, we explored the incidence of newly diagnosed prediabetes among selected subjects with NGT to further elucidate the nature of the relationship between lung function and the development of DM.

**METHODS**

**Subjects**

The subjects were recruited from 1218 men who attended the Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center for general health checkups between April 1999 and March 2006. One hundred and sixty subjects were excluded, because they did not meet the following inclusion criteria: (1) between 40 and 59 years of age at the first examination, and able to perform both a 75 g oral glucose tolerance test (OGTT) and adequate spirometric measurements (146 subjects excluded); (2) no known respiratory disease (14 excluded). Data from the remaining 1058 subjects were used for a baseline cross-sectional analysis. For the longitudinal study, subjects were restricted to those who had NGT (365 excluded), and could be followed up for more than 20 months (133 excluded). The remaining 560 subjects were included. Among these subjects, 77 were receiving medication for hypertension, 43 for dyslipidaemia and 11 for hyperuricaemia. The distributions of these subjects among the quartiles of percent predicted value of %FVC and percent value of 1 s/FVC (FEV1/FVC ratio) were not significantly different.

The study was approved by the Ethical Committee of Kochi University.

**RESULTS**

**Baseline analysis**

At baseline, our study population (n=1058) consisted of 693 normal subjects, 93 with isolated IFG, 167 with IGT and 105 with DM. To examine the relationship between lung function parameters and impaired glucose metabolism, the subjects were divided into quartiles according to baseline %FVC and the FEV1/FVC ratio. Some parameters, including age, body mass index (BMI), systolic blood pressure and total cholesterol, differed significantly among the quartiles (table 1). After adjustment for these parameters, impaired glucose metabolism was significantly associated with %FVC (p<0.001), but not with the FEV1/FVC ratio (p=0.80). Specifically, IGT (p=0.04) and DM (p=0.008), but not isolated IFG (p=0.28), were associated with %FVC (table 2).
Frequencies of newly diagnosed prediabetes in subjects with NGT

After the observation period (mean±SD: 28.4 ±6.1 months), there were 44 subjects with isolated IFG and 58 with IGT among those previously categorised as NGT (n=560), but no subject developed DM. As shown in table 3, there were significant differences in several parameters at baseline, including height, BMI, systolic blood pressure and %FVC, but not in FEV₁/FVC ratio.

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Table 1  Baseline characteristics of subjects with NGT, isolated IFG, IGT and DM in the cross-sectional study

|                        | NGT | Isolated IFG | IGT | DM | p Value |
|------------------------|-----|--------------|-----|----|---------|
| Number of subjects     | 693 | 93           | 167 | 105|         |
| Current smokers (%)    | 48  | 42           | 45  | 50 | 0.54    |
| Age (years)            | 49.5±5.5 | 50.9±5.3*   | 51.1±5.3** | 52.2±4.7*** | <0.001 |
| Height (cm)            | 169.9±5.7 | 168.8±5.8   | 169.1±6.0 | 168.4±5.0*  | 0.03   |
| BMI (kg/m²)            | 23.1±2.5  | 23.9±3.1**  | 24.6±2.8*** | 24.8±3.2*** | <0.001 |
| Systolic BP (mm Hg)    | 126.4±16.3 | 135.1±16.4*** | 135.9±18.3**** | 140.2±16.3*** | <0.001 |
| Pack-year smoking      | 30.5±15.6 | 38.0±22.6*   | 31.1±17.3 | 38.0±18.5** | 0.002  |
| FEV₁/FVC (%)           | 80.1±7.0  | 79.6±7.8     | 80.9±7.4 | 79.4±8.5  | 0.36   |
| %FVC                   | 97.9±14.2 | 96.5±12.9    | 92.0±13.3*** | 89.2±15.7*** | <0.001 |
| Fasting glucose (mmol/l)| 5.3±0.4  | 6.3±0.2***   | 5.9±0.5***  | 8.1±1.6***  | <0.001 |
| 120 min glucose (mmol/l)| 5.7±1.0  | 6.5±0.8***   | 8.8±0.8***  | 12.4±4.0*** | <0.001 |
| HbA1c (%)              | 5.10±0.33 | 5.34±0.36*** | 5.37±0.41*** | 6.57±1.20*** | <0.001 |
| HOMA-R                 | 1.08±0.56 | 1.91±2.23**  | 1.56±0.88*** | 2.33±1.41*** | <0.001 |
| C reactive protein (mg/l)| 0.11±0.29 | 0.09±0.14    | 0.14±0.28  | 0.18±0.46  | 0.13   |
| T-chol (mg/dl)         | 202.1±32.6| 210.0±28.7*  | 209.5±36.3* | 214.8±32.3*** | <0.001 |

Values are numbers, percentages (%) or means ±SD.
*p<0.05.
**p<0.01.
***p<0.001 vs NGT.

BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DM, diabetes mellitus; HbA1c, glycated haemoglobin; HOMA-R, homeostasis model assessment of insulin resistance; IFG, increased fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T-chol, total cholesterol.

Table 2  ORs*(95% CI) of prediabetes and DM according to the quartiles of %FVC† or FEV₁/FVC‡ in the cross-sectional study

|               | I           | II          | III         | IV          | p for trend |
|---------------|-------------|-------------|-------------|-------------|------------|
| IFG %FVC      | 1.0         | 4.60 (1.29 to 16.39) | 2.03 (0.53 to 7.79) | 2.57 (0.69 to 9.60) | 0.06       |
| IFG FEV₁/FVC  | 1.0         | 1.00 (0.32 to 3.12) | 1.39 (0.49 to 3.93) | 1.81 (0.67 to 4.90) | 0.53       |
| IGT %FVC      | 1.0         | 1.35 (0.57 to 3.19) | 2.18 (1.02 to 4.05) | 2.59 (1.17 to 5.69) | 0.04       |
| IGT FEV₁/FVC  | 1.0         | 0.60 (0.35 to 1.15) | 0.62 (0.37 to 1.16) | 0.50 (0.30 to 1.02) | 0.12       |
| IFG or IGT %FVC| 1.0         | 2.18 (1.08 to 4.42) | 2.09 (1.04 to 4.18) | 2.55 (1.28 to 5.09) | <0.001     |
| IFG or IGT FEV₁/FVC| 1.0         | 0.56 (0.31 to 1.07) | 0.63 (0.35 to 1.14) | 0.65 (0.36 to 1.17) | 0.29       |
| DM %FVC       | 1.0         | 3.77 (1.29 to 11.03) | 1.28 (0.41 to 3.99) | 2.50 (0.87 to 7.16) | 0.02       |
| DM FEV₁/FVC   | 1.0         | 2.08 (0.72 to 5.99) | 3.05 (1.12 to 8.31) | 2.13 (0.76 to 6.00) | 0.18       |
| IFG or IGT, or DM %FVC | 1.0         | 3.32 (1.71 to 6.42) | 2.04 (1.06 to 3.94) | 3.33 (1.74 to 6.38) | <0.001     |
| IFG or IGT, or DM FEV₁/FVC | 1.0         | 0.74 (0.40 to 1.35) | 0.98 (0.56 to 1.75) | 0.84 (0.48 to 1.49) | 0.70       |

*OR was adjusted for age, BMI, pack-year smoking, systolic BP and T-chol.
†%FVC quartile; I (highest group) (≥104.2%), II (96.0%≤%FVC<104.2%), III (86.4%≤%FVC<96.0%), IV (lowest group) (%FVC<86.4%).
‡FEV₁/FVC quartile; I (highest group) (≥85.0), II (81.1%≤FEV₁/FVC<85.0%), III (76.5%≤FEV₁/FVC<81.1%), IV (lowest group) (FEV₁/FVC<76.5%).

BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T-chol, total cholesterol.

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Low lung volume is a risk factor for prediabetes on September 1, 2023 by guest. Protected by copyright.
Lung function parameters were divided into quartiles according to baseline %FVC and the FEV1/FVC ratio. The incidence of prediabetes was significantly associated with %FVC, but not with the FEV1/FVC ratio (p=0.01). Among subjects with prediabetes, lower %FVC was significantly associated with a higher incidence of IGT (p=0.04), but not of IFG (p=0.47).

DISCUSSION

In the baseline cross-sectional study, we found that a low %FVC, but not a low FEV1/FVC ratio, was significantly associated with increased prevalences of prediabetes and DM. As lung function might be impaired by DM, a causal effect of lung function on DM could not be established by these data. Therefore, we also explored prospectively the effect of lung function on the development of newly diagnosed prediabetes in the population with normal glucose metabolism, as evidenced by the results of an OGTT. We found that reduced lung volume (%FVC), but not airflow limitation (FEV1/FVC ratio), was significantly associated with the future development of prediabetes.

This study demonstrated that IGT, but not IFG, was closely associated with lower lung volume in both cross-sectional and longitudinal settings. Our finding was supported by previous studies conducted in an Asian population with relatively low BMI but high smoking.

| Table 3 | Baseline characteristics of subjects who remained NGT, developed isolated IFG and IGT in the longitudinal study. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Number of subjects | NGT | Isolated IFG | IGT | p Value |
| Current smokers (%) | 458 | 44 | 58 | 0.05 |
| Age (years) | 49.3±5.7 | 50.2±4.4 | 50.5±4.9 | 0.14 |
| Height (cm) | 169.9±5.6 | 170.2±4.9 | 167.1±6.7** | 0.01 |
| BMI (kg/m²) | 23.0±2.5 | 23.8±2.3* | 23.7±3.0* | 0.04 |
| Systolic BP (mm Hg) | 125.4±16.7 | 130.5±16.9* | 129.3±14.5 | 0.048 |
| Pack-year smoking | 29.9±15.6 | 31.1±12.1 | 30.1±18.5 | 0.97 |
| FEV1/FVC (%) | 80.1±7.1 | 79.7±6.3 | 79.9±7.9 | 0.95 |
| %FVC (%) | 97.5±14.2 | 93.0±14.7* | 90.0±16.0*** | <0.001 |
| Fasting glucose (mmol/l) | 5.3±0.4 | 5.6±0.2** | 5.5±0.3** | <0.001 |
| 120 min glucose (mmol/l) | 5.6±0.9 | 6.0±1.2 | 6.4±0.9*** | <0.001 |
| HbA1c (%) | 5.07±0.33 | 5.31±0.37*** | 5.19±0.30* | <0.001 |
| HOMA-R | 1.04±0.53 | 1.19±0.61 | 1.31±0.64** | 0.001 |
| C reactive protein (mg/l) | 0.10±0.23 | 0.18±0.42 | 0.16±0.30 | 0.26 |
| T-chol (mg/dl) | 201.4±34.5 | 205.3±27.1 | 212.5±28.6* | 0.05 |
| Duration (month) | 28.6±6.2 | 28.5±5.1 | 27.6±5.6 | 0.13 |

Values are number, percentage (%) or mean±SD.

*p < 0.05.

**p < 0.01.

***p < 0.001 vs NGT.

BMI, body mass index; BP, blood pressure; CRP, C reactive protein; HOMA-R, homeostasis model assessment of insulin resistance; IFG, increased fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T-chol, total cholesterol.
In addition, such association between lower lung function and impaired glucose metabolism was also demonstrated in Western populations with higher BMI but lower smoking prevalence, and the association had been shown to be independent of smoking or obesity (refs.1–6, for review ref.7).

The mechanisms for the association are not clarified at present. It has been suggested that IGT is caused mainly by insulin resistance in the muscle, and IFG mainly by insulin resistance in the liver.25 Reduced lung volume is associated with reduced maximum oxygen uptake, which may lead to poorer physical fitness and physical activity, and thus result in insulin resistance and DM.26–28 This may explain why IGT is more closely associated with lung volume. Furthermore, poorer lung function in adulthood may be due to low birth weight or early-life malnutrition,29 30 both of which have been reported to be associated with the development of diabetes.31 Malnutrition as a neonate may be an important early cause of cardiac and metabolic disorders in adulthood as a consequence of fetal programming.32 33

This study had several limitations. The study population was limited to men, owing to the fact that sufficient female subjects were not available at the institute. The occupational cohort used in this study may not be representative of Japanese men in general. For example, the prevalence rates of hypertension and hyperlipidaemia in this cohort were 13% and 7%, respectively (data not shown). The National Health and Nutrition Examination Survey in Japan showed prevalence rate of these in general Japanese men aged 40–60 years, in general, were around 30% and 35%, suggesting that our occupational cohort may be healthier.

In conclusion, this study provides evidence for a prospective relationship between lung volume and the incidence of newly diagnosed prediabetes among subjects with normal glucose metabolism at baseline. Among subjects with prediabetes, the study also suggests that lung volume may be a risk factor for the development of IGT, which is mainly caused by insulin resistance in the

| Table 4 | HRs (95% CI) for development of isolated IFG or IGT according to the quartiles of %FVC* or FEV1/FVC†
|---------|------------------|------------------|------------------|------------------|
|         | I               | II              | III             | IV               | p for trend      |
| IFG     |                 |                 |                 |                  |                  |
| %FVC    |                 |                 |                 |                  |                  |
| Model 1 | 1.0             | 0.85 (0.38 to 1.92) | 0.81 (0.36 to 1.79) | 1.96 (0.71 to 5.26) | 0.31             |
| Model 2 | 1.0             | 1.07 (0.48 to 2.39) | 1.35 (0.60 to 3.03) | 0.54 (0.20 to 1.49) | 0.32             |
| FEV1/FVC|                 |                 |                 |                  |                  |
| Model 1 | 1.0             | 0.96 (0.42 to 2.17) | 1.20 (0.51 to 2.86) | 0.98 (0.43 to 2.27) | 0.95             |
| Model 2 | 1.0             | 0.99 (0.43 to 2.31) | 0.84 (0.35 to 2.00) | 1.04 (0.45 to 2.47) | 0.96             |
| IGT     |                 |                 |                 |                  |                  |
| %FVC    |                 |                 |                 |                  |                  |
| Model 1 | 1.0             | 1.96 (1.00 to 3.85) | 2.63 (1.27 to 5.56) | 3.03 (1.43 to 6.67) | 0.006            |
| Model 2 | 1.0             | 2.22 (1.02 to 3.88) | 2.26 (1.07 to 4.78) | 2.74 (1.26 to 5.98) | 0.02             |
| FEV1/FVC|                 |                 |                 |                  |                  |
| Model 1 | 1.0             | 2.13 (0.96 to 4.76) | 1.67 (0.81 to 3.45) | 1.03 (0.54 to 1.96) | 0.15             |
| Model 2 | 1.0             | 2.09 (0.92 to 4.72) | 1.69 (0.81 to 3.52) | 1.11 (0.57 to 2.16) | 0.10             |
| IFG or IGT|             |                 |                 |                  |                  |
| %FVC    |                 |                 |                 |                  |                  |
| Model 1 | 1.0             | 2.13 (0.93 to 3.03) | 1.85 (1.03 to 3.57) | 2.63 (1.43 to 4.76) | 0.01             |
| Model 2 | 1.0             | 1.48 (0.89 to 2.44) | 1.38 (0.82 to 2.34) | 2.40 (1.30 to 4.44) | 0.04             |
| FEV1/FVC|                 |                 |                 |                  |                  |
| Model 1 | 1.0             | 1.47 (0.84 to 2.56) | 1.47 (0.85 to 2.56) | 1.01 (0.61 to 1.69) | 0.32             |
| Model 2 | 1.0             | 1.47 (0.83 to 2.61) | 1.47 (0.84 to 2.56) | 1.09 (0.64 to 1.84) | 0.21             |

*%FVC quartile; I (highest group) (≥106.0%), II (96.6%<%FVC<106.0%), III (88.1%<%FVC<96.6%), IV (lowest group) (%FVC<88.1%).
†FEV1/FVC quartile; I (highest group) (≥85.0%), II (80.9%<FEV1/FVC<85.0%), III (76.0%<FEV1/FVC<80.9%), IV (lowest group) (FEV1/FVC<76.0%).

IGT, impaired glucose tolerance; IFG, increased fasting glucose.
Model 1 denotes crude model and model 2, adjusted for age, BMI, pack-year smoking and systolic BP.
muscle, but not IFG, which is caused mainly by insulin resistance in the liver. Although there is published evidence for an association between COPD and DM, our results suggest that prediabetes is not associated with at least the early stage of COPD.

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