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ORIGINAL ARTICLE

The association between glycemic control and lung function impairment in individuals with diabetes: the Saku study

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Abstract

Aim Though diabetes is a risk factor for lung function impairment, whether the glycemic control level affects lung function in individuals with diabetes remains unclear. The present study aimed to assess the association between glycemic control level and restrictive or obstructive lung function impairment in individuals with diabetes.

Methods This cross-sectional study included 1028 individuals with diabetes, aged 40–69 years, who underwent a medical checkup between April 2008 and March 2014. Hemoglobin A1c (HbA1c) was categorized as < 6.9%, 7.0–7.9%, and ≥ 8.0%. Restrictive and obstructive lung function impairment was defined by a forced vital capacity (FVC) < 80% predicted and a forced expiratory volume in 1 s to FVC ratio < 0.70.

Results Of the participants, 8.7% and 6.3% were classified as having restrictive and obstructive lung function impairment, respectively. The multivariable-adjusted odds ratios and 95% confidence intervals for restrictive lung function impairment were 1.43 (0.84–2.42) in individuals with HbA1c 7.0–7.9%, and 2.42 (1.38–4.26) in individuals with HbA1c ≥ 8.0%, compared with those who had HbA1c < 6.9% (p for trend = 0.002). In contrast, glycemic control level was not associated with obstructive lung function impairment (p for trend = 0.749).

Conclusions Poor glycemic control was associated with restrictive lung function impairment in individuals with diabetes. Good glycemic control would be important to minimize restrictive lung function impairment in individuals with diabetes.

Keywords Restrictive lung function impairment · Obstructive lung function impairment · Glycemic control · HbA1c

Introduction

A recent cohort study of 30,834 Japanese patients with diabetes showed that those who had a history of chronic restrictive or obstructive lung diseases had a 1.6-fold higher risk of mortality than those who did not [1]. Therefore, it is important to prevent the development of chronic restrictive or obstructive lung diseases in patients with diabetes.

Regarding the association between diabetes and lung function impairment, a meta-analysis of cross-sectional studies demonstrated that individuals with diabetes have lower forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) than those without diabetes [2]. In addition, our large cohort study conducted in Japan showed that individuals with diabetes have a 1.6-fold higher risk of developing restrictive lung function impairment than those without diabetes, after adjusting for confounding factors [3]. Thus, the presence of diabetes appears to be a risk factor for lung function impairment, but it is unclear whether the

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glycemic control level affects lung function in individuals with diabetes. Since glycemic control is critical in diabetes care, determining the glycemic control level that is associated with lung function impairment is likely to be important in preventing lung function impairment in people with diabetes.

The present study, therefore, aimed to assess the association between glycemic control level and restrictive or obstructive lung function impairment in individuals with diabetes.

Methods

Study participants

The details of this study have been described previously [3–5]. This cross-sectional study included 1178 individuals with diabetes, aged 40–69 years, who underwent an initial 1- or 2-day comprehensive medical checkup between April 2008 and March 2014 at Saku Central Hospital. The presence of diabetes was defined by a history of diabetes (including having received treatment for diabetes or having taken antidiabetic medication), determined by a physician at an interview. Of the 1178 individuals with diabetes, we excluded three individuals who had a history of pulmonary surgery and five who had respiratory disease (pulmonary fibrosis, anthracotic tuberculosis, old lung tuberculosis, pulmonary emphysema, or chronic bronchitis), determined by X-ray or computed tomography. We also excluded 124 individuals who had a past or present history of coronary heart disease, cardiac heart disease, and cerebrovascular disease, and 18 individuals with missing data. Thus, 1028 individuals with diabetes were analyzed.

The study protocol was written in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Saku Central Hospital Group (date of approval 24 October 2016; approval no. R201404-02) and Osaka University (date of approval 21 December 2016; approval no. 16060-2). An opt-out consent procedure was implemented. The standard questionnaires included opt-out information.

Data collection

Blood samples were obtained in the morning after a 10-h overnight fast. Hemoglobin A1c (HbA1c) was used as an index of glycemic control. HbA1c concentration was measured using high-performance liquid chromatography. HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program equivalent value (%) and calculated using the formula HbA1c (%) = 1.02 × HbA1c (Japan Diabetes Society, %) + 0.25% [6]. HbA1c was categorized as < 6.9%, 7.0–7.9%, and ≥ 8.0%, which was used as an index of glycemic control.

Each checkup involved the completion of standard questionnaires regarding demographic characteristics, medical history, and health-related habits. Smoking status was categorized as non-smoker, ex-smoker, and current smoker. Current and ex-smokers were asked to report on the average number of cigarettes smoked or had smoked per day and the duration of smoking in years. To consider the cumulative smoking exposure in current and ex-smokers, pack-years were calculated. A pack-year was defined as smoking 20 cigarettes/day for one year. Participants were categorized by the number of pack-years into the following three groups: 0 pack-years (non-smoker), 0.1–19.9 pack-years, and ≥ 20 pack-years. Exercise habits (at least twice a week, ≥ 30 min on each occasion) were categorized as presence and absence. Waist circumference, weight, and height were measured in the fasting state. Waist circumference was measured around the abdomen at the level of the navel, during the late expiratory phase, in the standing position, with a tape measure. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Hypertension was defined by a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [7], and/or patients receiving medical treatment for hypertension. Dyslipidemia was defined by a plasma high-density lipoprotein cholesterol < 40 mg/dl, and/or low-density lipoprotein cholesterol ≥ 140 mg/dl, and/or triglycerides ≥ 150 mg/dl [8], and/or patients receiving medical treatment for dyslipidemia.

Definition of lung function impairment

Spirometry was performed by trained laboratory technicians according to the guidelines of the American Thoracic Society and the Japanese Respiratory Society, using a multifunctional spirometer HI-801 (CHEST M.I., Inc., Tokyo, Japan) [9]. Before initiating the test, its purpose and methodology were explained to the participants. During the test, participants were in the seated position with a nose-clip in place. After the participants had been trained for the test at least once, FVC and FEV_1 were measured twice. The better of the two recordings was used. FVC% predicted was calculated using the formula: FVC% predicted = FVC/predicted FVC × 100 [9]. Predicted FVC was calculated using the formula suggested by the Japanese Respiratory Society: predicted FVC for men = exp [− 8.8877 + 2.1494 × Ln (height) − 0.1891 × Ln (age) + (M-spline value by age)] and predicted FVC for women = exp [− 8.3268 + 2.0137 × Ln (height) − 0.2029 × Ln (age) + (M-spline value by age)] [10]. Restrictive lung function impairment was defined as FVC < 80% predicted and FEV_1/FVC ≥ 0.70 [9], obstructive lung function impairment was defined as FVC ≥ 80% predicted and an FEV_1/FVC < 0.70 [9], and mixed

restrictive-obstructive lung function impairment was defined as an FVC < 80% predicted and $FEV_1/FVC < 0.70$ [9].

Statistical analysis

Differences in the characteristics of individuals with diabetes according to the HbA1c category (< 6.9%, 7.0–7.9%, and ≥ 8.0%) were identified using analysis of variance for continuous data with a normal distribution, and using the χ^2 test for dichotomous and categorical data.

The proportions of individuals with diabetes who had restrictive or obstructive lung function impairment, classified according to the glycemic control level, were compared using the χ^2 test. In addition, to identify the association between glycemic control level and restrictive or obstructive lung function impairment in individuals with diabetes, multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression analysis. Sex (men or women), age, pack-years of smoking (0 pack-years, 0.1–19.9 pack-years, or ≥ 20 pack-years), exercise habits (presence or absence), waist circumference, and dyslipidemia (presence or absence) were included in the model.

All data were analyzed using SPSS (version 25; Japan IBM, Tokyo, Japan). All reported p values are two-tailed and $p < 0.05$ was considered to represent statistical significance.

Results

Characteristics of individuals with diabetes according to the glycemic control level

The mean age of the 1028 (732 men and 296 women) participants was 58.4 years and their mean HbA1c was 7.1%. Table 1 shows the characteristics of individuals with diabetes according to the HbA1c category. Age, waist circumference, BMI, and dyslipidemia differed significantly among the three groups.

Classification of participants according to the lung function status

Of the participants, 862 (83.9%) were classified as having normal lung function (FVC ≥ 80% predicted and $FEV_1/FVC \geq 0.70$), 89 (8.7%) were classified as having restrictive lung function impairment (FVC < 80% predicted and $FEV_1/FVC \geq 0.70$), 65 (6.3%) were classified as having obstructive lung function impairment (FVC ≥ 80% predicted and $FEV_1/FVC < 0.70$), and 12 (1.2%) were classified as having mixed restrictive-obstructive lung function impairment (FVC < 80% predicted and $FEV_1/FVC < 0.70$).

Table 1 Characteristics of 1028 individuals with diabetes according to the HbA1c category

Variable	HbA1c			p value
	< 6.9%	7.0–7.9%	≥ 8.0%	
n	579	285	164	
Men	70.5	70.5	75.0	0.504
Age (years)	58.9 ± 6.2	58.6 ± 6.3	56.3 ± 7.1	<0.001
Pack-years of smoking				0.432
0 pack-years (non-smoker)	40.1	41.4	35.4	
0.1–19.9 pack-years	17.8	14.7	15.2	
≥ 20 pack-years	42.1	43.9	49.4	
Exercise habits	29.2	25.6	20.1	0.060
Waist circumference	85.7 ± 8.5	88.0 ± 9.0	90.0 ± 10.6	<0.001
Body mass index	23.9 ± 3.3	24.9 ± 3.7	26.0 ± 4.3	<0.001
Hypertension	47.8	51.6	43.9	0.280
Dyslipidemia	53.4	59.3	64.6	0.022

Hypertension was defined by a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or patients receiving medical treatment for hypertension

Dyslipidemia was defined by a high-density lipoprotein cholesterol < 40 mg/dl and/or low-density lipoprotein cholesterol ≥ 140 mg/dl and/or triglycerides ≥ 150 mg/dl, and/or patients receiving medical treatment for dyslipidemia

Continuous data were evaluated using analysis of variance, and are shown as mean ± standard deviation

Dichotomous and categorical data were analyzed using the χ^2 test, and are shown as %

HbA1c hemoglobin A1c

Association between glycemic control level and restrictive lung function impairment in individuals with diabetes

Table 2 shows the multivariable-adjusted ORs and 95% CIs for having restrictive lung function impairment, classified according to the HbA1c category. The proportions of individuals with diabetes who had restrictive lung function impairment, according to the HbA1c category, were 6.8% in those with HbA1c < 6.9%, 10.2% in those with HbA1c 7.0–7.9%, and 17.1% in those with HbA1c ≥ 8.0% ($p = 0.001$). The multivariable-adjusted ORs and 95% CIs for having restrictive lung function impairment were 1.43 (0.84–2.42) in those with HbA1c 7.0–7.9%, and 2.42 (1.38–4.26) in those with HbA1c ≥ 8.0%, compared with those with HbA1c < 6.9% (p for trend = 0.002). In multivariable analysis, waist circumference was also associated with restrictive lung function impairment. This result did not change when BMI was adjusted instead of waist circumference. The multivariable-adjusted ORs and 95% CIs for having restrictive lung function impairment were 1.43 (0.84–2.44) in those with HbA1c 7.0–7.9% and 2.44

Table 2 Multivariable-adjusted odds ratios and 95% confidence intervals for restrictive and obstructive lung function impairment, classified according to the HbA1c category

Variable	Restrictive lung function impairment[a] (FVC < 80% predicted) Odds ratio (95% CI)	Obstructive lung function impairment[b] (FEV_1/FVC < 0.70) Odds ratio (95% CI)
HbA1c category (vs. < 6.9%)		
7.0–7.9%	1.43 (0.84–2.42)	0.97 (0.52–1.78)
≥ 8.0%	2.42 (1.38–4.26)	1.20 (0.55–2.65)
Men (vs. women)	0.81 (0.41–1.60)	1.29 (0.48–3.51)
Age	1.02 (0.98–1.06)	1.13 (1.07–1.19)
Pack-years of smoking (vs. 0 pack-years)		
0.1–19.9 pack-years	1.01 (0.46–2.23)	2.26 (0.81–6.36)
≥20 pack-years	1.45 (0.74–2.82)	3.90 (1.57–9.73)
No exercise habits (vs. exercise habits)	0.80 (0.47–1.37)	0.72 (0.41–1.27)
Waist circumference	1.04 (1.01–1.06)	0.99 (0.96–1.03)
Dyslipidemia (vs. non-dyslipidemia)	1.53 (0.94–2.49)	0.99 (0.58–1.70)

Model: Adjusted for sex, age, pack-years of smoking (0 pack-years, 0.1–19.9 pack-years, or ≥ 20 pack-years), exercise habits (presence or absence), waist circumference, and dyslipidemia (presence or absence)

HbA1c hemoglobin A1c

[a]We excluded 77 individuals with obstructive lung function impairment

[b]We excluded 101 individuals with restrictive lung function impairment

(1.39–4.30) in those with HbA1c ≥ 8.0% compared with those with HbA1c < 6.9% (p for trend = 0.002) (S1 Table).

In an additional analysis, we confirmed HbA1c values in 2007 among individuals with diabetes who underwent an initial 1- or 2-day comprehensive medical checkup in 2008. Glycemic control levels were categorized using HbA1c values in 2007 and 2008 (two HbA1c measurements) among 384 individuals with diabetes who did not change their HbA1c category from 2007 to 2008. The multivariable-adjusted ORs and 95% CIs for having restrictive lung function impairment were 1.90 (0.64–5.62) in those with persistent HbA1c 7.0–7.9% and 4.74 (1.49–15.13) in those with persistent HbA1c ≥ 8.0% compared with those with persistent HbA1c < 6.9% (p for trend = 0.009) (S2 Table).

Association between glycemic control level and obstructive lung function impairment in individuals with diabetes

Table 2 shows the multivariable-adjusted ORs and 95% CIs for having obstructive lung function impairment, classified according to the HbA1c category.

The proportions of individuals with diabetes who had obstructive lung function impairment, according to the HbA1c category, were 7.3% in individuals with HbA1c < 6.9%, 6.6% in those with HbA1c 7.0–7.9%, and 6.7% in those with HbA1c ≥ 8.0% (p = 0.934). The multivariable-adjusted ORs and 95% CIs for having obstructive lung function impairment were 0.97 (0.52–1.78) in individuals with HbA1c 7.0–7.9%, and 1.20 (0.55–2.65) in those with HbA1c ≥ 8.0%, compared with those with HbA1c < 6.9% (p for trend = 0.749). In multivariable analysis, age and pack-years of smoking were associated with obstructive lung function impairment.

Discussion

The main findings of the present study were that glycemic control level is associated with having restrictive lung function impairment in individuals with diabetes but it is not associated with having obstructive lung function impairment.

Regarding restrictive lung function impairment, previous studies have reported that abdominal obesity was associated with restrictive lung function impairment [11, 12]. In this study, individuals with diabetes who had HbA1c ≥ 8.0% had a 2.4-fold higher risk of having restrictive lung function impairment than those with HbA1c < 6.9%, after adjusting for confounding factors, including waist circumference. Therefore, it is thought that glycemic control level is associated with restrictive lung function impairment, independently from waist circumference. Recently, we revealed that individuals with diabetes had a higher risk of developing restrictive lung function impairment than those without diabetes [3]. Thus, these studies suggest that the presence of diabetes is a risk factor of restrictive lung function impairment, and poor glycemic control in individuals with diabetes is associated with elevated risk of restrictive lung function impairment. Although the mechanisms underlying the relationship between glycemic control level and having

restrictive lung function impairment remain unclear, it has been reported that diabetes is associated with a decline in the strength and endurance of respiratory muscles, particularly the diaphragm [13–15]. In addition, a previous study reported a negative association between high HbA1c and lower respiratory muscle mass [15]. Therefore, poor glycemic control may affect a decline in the strength and endurance of respiratory muscles, and this process may lead to restrictive lung function impairment. However, whether this is the case or not, good glycemic control is likely to be important to minimize restrictive lung function impairment in individuals with diabetes.

This study had several limitations. First, because it was cross-sectional, it is not capable of establishing causality. Therefore, a further prospective investigation is necessary. Second, there may have been a possibility of selection bias, because the participants in this study were individuals who were undergoing routine comprehensive medical checkups. Although these checkups are generally expensive in Japan, those at Saku Central Hospital are relatively inexpensive or free, because administrations and employers subsidize their costs. Third, glycemic control levels were categorized using HbA1c values that were measured only once. Therefore, we conducted an additional analysis using HbA1c values in 2007 and 2008. The results did not change in this additional analysis. Fourth, we did not evaluate the effects of the duration of diabetes, the presence of complications, or diabetes treatment including insulin therapy and oral hypoglycemic agents. A future study should also consider these factors in its design. Finally, we did not assess any muscular strength. Therefore, a further investigation that considers muscular strength is necessary.

Despite these potential limitations, the present findings support the conclusion that poor glycemic control was associated with restrictive lung function impairment in individuals with diabetes. Therefore, good glycemic control would be important to minimize restrictive lung function impairment in individuals with diabetes.

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Author contributions NS participated in the design of the study, analyzed data and wrote the manuscript. AM, YT, KA, TO, and YO participated in the design of the study, and contributed to the writing and editing of the manuscript. SI collected data, and contributed to the writing and editing of the manuscript. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights and animal participants All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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