DSX 17 (2023) 102831

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Associations between spirometric measures and exercise capacity in type 2 diabetes

Charles Antwi-Boasiako [a,b], Mulbah Fasama Kollie [a,c], Kumi Ampaabeng Kyeremeh [a], Josephine Korang Osei-Tutu [a], Latif Musah [a], Patience Vormatu [d], Ruth Korkor Tei [e], Tracy Hanson [a], Sylvia Esther Sackitey-Ninye [a], Theresa Ruby Quartey-Papafio [h], Charles F. Hayfron-Benjamin [a,f,g,h,*]

[a] Department of Physiology, University of Ghana Medical School, Ghana
[b] College of Nursing, University of Wisconsin-Milwaukee, United States
[c] AM Dogliotti College of Medicine, University of Liberia, Liberia
[d] Department of Biomedical Sciences, University of Cape Coast, Ghana
[e] Department of Medicine and Therapeutics, University of Ghana Medical School, Ghana
[f] Department of Respiratory Medicine and Department of Pediatric Respiratory Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands
[g] Department of Internal and Vascular Medicine, Amsterdam UMC, University of Amsterdam, Cardiovascular Sciences, Amsterdam, the Netherlands
[h] Department of Anaesthesia and Critical Care, University of Ghana Medical School and Korle Bu Teaching Hospital, Ghana

ARTICLE INFO

Keywords:
Diabetes
Submaximal exercise capacity
Six-minute walk test
Spirometry
Pulmonary function

ABSTRACT

Background: Physical exercise aids glycemic control and the prevention of diabetes-related complications. However, exercise beyond an individual's pulmonary functional capacity may be detrimental. To date, little is known about the relationship between pulmonary function and exercise capacity in people with type 2 diabetes (T2D). We investigated the relationship between pulmonary function and exercise capacity in T2D.

Methods: Spirometry and 6-min walk test (6MWT) were conducted for 263 systematically sampled adults with T2D without primary heart/lung disease. The primary measure of exercise capacity was the 6-min walk distance (6MWD); impaired exercise capacity was defined as 6MWD<400 m. Logistic regression analyses were used to assess the associations between spirometric measures and exercise capacity with adjustments for age, sex, height, body mass index, diabetes duration, glycated hemoglobin concentration, smoking, suboptimum blood pressure control, and total cholesterol concentration.

Results: Compared with individuals with normal spirometry, those with pulmonary restriction/obstruction had significantly lower 6MWD (404.67 m vs. 451.70),$p < 0.001$). The proportion of individuals with impaired exercise capacity was higher in individuals with impaired pulmonary function compared with those with normal pulmonary function (39.8% vs. 20.7%,$p = 0.001$). In the unadjusted models, decreasing Z-score FEV_1 [odds ratio 1.40, 95% confidence interval (1.07–1.83),$p = 0.013$] and Z-score FVC [1.37 (1.06–1.76),0.016], but not Z-score FEV_1/FVC ratio [1.00 (0.78–1.27),0.972] were significantly associated with impaired exercise capacity. In the fully adjusted model, the strength of association remained statistically significant for Z-score FEV_1 [1.60 (1.06–2.41),0.025] but not Z-score FVC [1.48 (0.98–2.23),0.065].

Conclusions: Our study shows inverse associations between FEV_1 and impaired exercise capacity in T2D, Future research could characterize optimal exercise levels based on a patient's FEV_1.

1. Introduction

Globally, diabetes remains highly prevalent [1]. For example, in 2021, the global prevalence of diabetes in individuals aged 20–79 years was 10.5% (536.6 million people); this is projected to rise to 12.2% (783.2 million) in 2045 [1]. The overwhelming majority of people with diabetes in 2021 had type 2 diabetes (T2D) and the increases to 2045 are projected to be similarly predominantly of T2D [1]. Individuals with T2D are at increased risk of both vascular complications, which are causes of disability, repeated hospitalization, and early mortality [2,3].

* Corresponding author. Department of Physiology, University of Ghana Medical School, Ghana.
E-mail addresses: charlesfhb1@gmail.com, c.hayfronbenjamin@amsterdamumc.nl (C.F. Hayfron-Benjamin).

https://doi.org/10.1016/j.dsx.2023.102831

Available online 18 July 2023

Impaired glycemic control is a key modifiable risk factor for vascular complications in T2D [2,4]. Improving glycemic control has been shown to decrease the risk of diabetes-related vascular complications [5].

An effective and less expensive non-pharmacological therapy for achieving optimal glycemic control is physical exercise [6]. Mechanistically, there is an augmentation in insulin sensitivity of the muscles during exercise, thus promoting glycogen resynthesis from glucose and hence improving glycemic control [6]. For example, a single session of exercise has proven to improve glucose uptake via both insulin-mediated and non-insulin-mediated glucose uptake processes [6], and the increased insulin sensitivity following exercise can last for up to 48 h [6]. Although exercise is valuable to achieving optimal glycemic control and prevention of disease complications, exercise beyond an individual's pulmonary functional capacity may be detrimental. This is especially important in individuals with T2D where pulmonary function may be compromised; a recent meta-analysis has reported that T2D is associated with impaired pulmonary function, independently of sex, smoking, BMI, and geographical region [7]. Given the potential impact of lung function on exercise tolerance, previous studies have assessed the relationships between measures of pulmonary function including forced expiratory volume in 1 s (FEV_1) with measures of exercise capacity including the 6-min walk distance (6MWD) in some patient populations including chronic obstructive pulmonary disease [8] and cystic fibrosis [9]. Evidence shows that this relationship is dependent on the patient population. For example, Santos et al. [10] had previously reported no correlation between FEV_1 and 6MWD in individuals with severe/very severe airway obstruction.

To the best of our knowledge, no prior study has reported the association between pulmonary function and exercise capacity in people with T2D, who are relevantly different from individuals with primary lung diseases like COPD. For example, the cardiac contribution to impaired exercise tolerance in people with T2D may be from coronary artery disease [2] while that in chronic lung disease may be from group 3 pulmonary hypertension [11]. Cardiovascular-related factors that limit exercise capacity [12] are commoner in people with T2D compared with those without diabetes [13]. Besides, the biological basis of lung disease in T2D differs substantially from that in individuals with primary lung disease [7,14,15]. Kuziemski et al. [16] had recently reported functional exercise capacity and pulmonary functional capacity arrangements in patients with diabetes; compared with healthy controls. In their study, patients with diabetes were found to have shorter 6MWD and lower FEV_1. While Kuziemski et al. [16] reported reductions in both 6MWD and lower FEV_1, the associations between them, and how this association is impacted by the conventional cardiopulmonary risk factors remain unknown. We, therefore, investigated the relationship between pulmonary function (based on spirometric indices) and exercise capacity (based on the 6-min walk test [6MWT]) in people with T2D, and the impact of conventional diabetes and cardiopulmonary risk factors on this association. We tested the hypothesis that impaired pulmonary function based on a reduction in the FEV_1 is associated with impaired exercise capacity based on the 6MWT. Our primary measure of impaired pulmonary function was a reduction in FEV1 because previous studies show that compared with FVC or the presence of obstructive/restrictive pulmonary defects, FEV_1 is a better predictor of adverse cardiovascular events and/or mortality [17–19]. Exercise capacity was based on the 6MWT, which assesses submaximal exercise capacity because it more closely approximates the capacity to perform activities of daily living [20]. Both spirometry and 6MWT do not require sophisticated equipment and can be performed by most patients [20,21].

2. Methods

2.1. Study design

This cross-sectional study among 500 adults with T2D managed at a National Diabetes Management and Research Centre in Ghana has been previously described [22,23]. Individuals with primary heart disease and/or previous/current heart failure were also excluded from the study [22,23]. The current analyses included 263 participants aged ≥35 years with technically acceptable spirometry data, who performed the 6MWT, and with no history of primary lung disease including asthma or chronic obstructive pulmonary disease (COPD). Ethical approval was obtained from the Ethics and Protocol Review Committees of the University of Ghana College of Health Sciences (CHS–Et/M6-P2.14/2017–2018) and the Institutional Review Board of the Korle Bu Teaching Hospital (KBTH-IRB/000124/2019). All participants provided written informed consent before enrolment in the study.

2.2. Measurements

Assessment of baseline clinical characteristics including smoking and diabetes duration, anthropometry, hemodynamic monitoring, and biochemical measurements including the concentrations of fasting plasma glucose, HbA1c, and lipids has also been previously described [23]. The definition of hypertension was based on a clinical diagnosis code/documentation in the medical records, evidenced by documented elevated BP(≥140/90 mmHg) at the time of diagnosis, and the use of antihypertensive therapy. Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP>/ = 130 mmHg and/or diastolic BP>/ = 80 mmHg [24]. These cutoff values are consistent with the American Diabetes Association's recommendation (2018 update) for individuals with diabetes with higher cardiovascular risk [25].

2.3. Pulmonary function testing

Spirometry was conducted by trained physicians/technicians using the Vitalograph Pneumotrac Portable Screening Pneumotachograph (Morgan Scientific) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [21]. Measured and calculated indices included the FEV_1, forced vital capacity (FVC), and the FEV_1/FVC ratio. The predicted values of the FEV_1, FVC, and FEV_1/FVC were determined for each participant using the Global Lung Function Initiative 2012 equations [26]. Abnormal results for spirometric indices were determined by comparison to their lower limits of normal (LLN) [26]. The values of FEV_1/FVC and FVC were used to categorize pulmonary function patterns as normal, obstructive, restrictive, or mixed obstructive and restrictive based on ATS/ERS guidelines according to a modified algorithm based on Pellegrino et al. [27]. Due to heterogeneity in individuals with impaired spirometry, we analyzed FEV_1, FVC, and FEV_1/FVC as a continuous variable via Z-score.

2.4. Six-minute walk test

The 6-min walk test (6MWT) is a simple but standardized test used to assess exercise tolerance [20]. The 6MWT was performed by trained physicians/technicians using the Nonin Modell 3150 WristOx2 pulsoximeter (Nonin Medical, USA) on a 20-m corridor with no prior practice walks according to the ATS guidelines [20]. Participants were instructed to walk to cover as much ground as possible in 6 min. Standardized encouragement at 1-min intervals was given. The primary measure of impaired exercise capacity was based on a reduction in the 6-min walk distance (6MWD) (6MWD<400 m) [28]. The percentage predicted 6MWD was not used in the current analyses because no population-specific equations were found for sub-Saharan Africans. HR was continuously monitored during the 6MWT, and the maximum HR during the test was recorded. To determine the effort made by the participants during the test, we recorded the maximal heart rate achieved by a participant during the test (HR_{max}) and expressed it as a percentage of the age-predicted maximum HR which was determined using the

formula predicted HR $_{\text{max age predicted}}$ = 220 – age in years. Hence, HR_{max} pp = 100 * HR_{max}/(220-age). We also assessed the elevated percentage predicted maximum HR (HR_{max} pp > 80).

2.5. Statistical analysis

Data were analyzed using IBM SPSS (Version 26) for Windows. Data with a normal distribution were presented as mean (± standard deviation whereas those not normally distributed were presented as median (interquartile range). Categorical data were presented as frequencies (percentages). Differences in clinical characteristics between individuals with normal and abnormal spirometry were assessed by the chi-square test or Fisher's exact test for categorical variables, t-test for continuous variables, or the Mann-Whitney U-test for variables not normally distributed. Multivariate logistic regression analyses were used to examine the associations between decreasing z-score FEV_1, FVC, and FEV_1/FVC ratio (independent variable) and impaired exercise capacity (dependent variable), with adjustment for potential covariates (age, sex, height, BMI, diabetes duration, HbA1c concentration, smoking, suboptimum blood pressure control, and total cholesterol concentration). Odds ratios (ORs) and their corresponding 95% CI were estimated.

3. Results

3.1. General characteristics

The baseline characteristics of the study population are shown in Table 1. Compared with individuals with normal spirometry, individuals with impaired spirometry were more frequently females and much older. Individuals with impaired spirometry were also much shorter and had a longer mean duration of diabetes compared with individuals with normal spirometry. However, the two groups did not differ in terms of the proportion of individuals with hypertension, suboptimal BP control, obesity, higher education, or current/previous smokers. Similarly, there were no significant differences in the mean systolic BP, diastolic BP, and BMI between the two groups. Further, the two groups did not differ in terms of the mean HbA1c and lipid concentrations. Expectedly, the mean FEV_1 pp, FVC pp, and FEV_1/FVC were lower in individuals with impaired spirometry compared with those with normal spirometry.

3.2. 6MWT measures in the study population

Table 2 compares the 6MWT measures in the two study groups. The mean 6MWD was over 10% lower in individuals with impaired pulmonary function compared with those with normal pulmonary function (404.67 m vs. 451.70 m, p < 0.001). Also, the proportion of individuals with 6MWD<400 m was nearly twice in individuals with impaired pulmonary function compared with those with normal pulmonary function (39.8% vs. 20.7%, p = 0.001). While the mean pre-6MWT SpO_2 was significantly lower in the impaired pulmonary function group compared with the normal pulmonary function group, the two groups did not significantly differ in the mean post-6MWT SpO_2 mean change in the SpO_2 during the test, and the mean lowest SpO_2 recorded during the test. Both the pre-and post-6MWT Borg dyspnea scores were higher in individuals with impaired pulmonary function compared with those with normal pulmonary function. Measures of heart rate including the mean pre-6MWT heart rate, mean post-6MWT heart rate, mean HR_{max} pp, and proportion of individuals with HR_{max} pp > 80 did not significantly differ between the two groups.

3.3. Association between spirometric measures and exercise capacity

Fig. 1 compares the proportion of individuals with impaired exercise capacity in individuals with and without pulmonary restriction or airway obstruction. The proportion of individuals with impaired exercise capacity was nearly twice as high in individuals with pulmonary restriction compared with individuals without pulmonary restriction (40.3% vs 21.6%, p = 0.002). While the proportion of individuals with impaired exercise capacity was 40% higher in individuals with airway obstruction compared with individuals without airway obstruction (36.8% vs 26.3%, p = 0.321), the difference was not statistically significant.

Table 3 shows the associations between Z score FEV_1, FVC, and

Table 1
Baseline characteristics of the study participants.

Characteristics	All Participants	Normal Pulmonary Function	Pulmonary Dysfunction[a]	*P*-Value
N	263	175	88	
Sex (%)				<0.001
Females	196 (74.5%)	115 (65.7%)	81 (92.0%)	
Males	67 (25.5%)	60 (34.3%)	7 (8.0%)	
Age (years)	57.28 (±9.83)	56.25 (±10.17)	59.31 (±6.53)	0.017
Education				0.164
Secondary/ higher	97 (47.3%)	74 (50.7%)	23 (39.0%)	
<Secondary	108 (52.7%)	72 (49.3%)	38 (61.0%)	
Smoking				1.000
Never smoked	259 (98.5%)	172 (98.3%)	87 (98.9%)	
Current/ previous smoker	4 (1.5%)	3 (1.7%)	1 (1.1%)	
Duration of diabetes (years)	11.23 (±6.23)	10.61 (±7.09)	12.76 (±6.37)	0.033
Hypertension (%)	126 (47.9%)	81 (46.3%)	45 (51.1%)	0.514
Systolic BP, mmHg	136.15 (±16.15)	135.90 (±15.94)	136.66 (±16.64)	0.720
Diastolic BP, mmHg	78.63 (±8.35)	78.91 (±8.01)	78.06 (±9.01)	0.439
Suboptimal BP control (%)	179 (68.1%)	115 (65.7%)	64 (72.7%)	0.266
Height, cm	163.79 (±8.49)	165.14 (±8.70)	161.09 (±7.39)	<0.001
BMI, kg/m^2	29.39 (±6.12)	29.71 (±5.90)	28.76 (±6.53)	0.236
Obesity (%)	105 (39.9%)	76 (43.4%)	29 (33.0%)	0.111
Biochemical measures				
HbA1c, %	8.12 (±1.84)	8.03 (±1.87)	8.31 (±1.77)	0.278
Total cholesterol, mmol/l	4.84 (±1.31)	4.77 (±1.33)	4.98 (±1.24)	0.240
Triglyceride, mmol/l	1.22 (±0.51)	1.24 (±.51)	1.19 (±.53)	0.553
HDL- cholesterol, mmol/l	1.34 (±0.35)	1.33 (±.35)	1.36 (±.35)	0.554
LDL-cholesterol, mmol/l	2.94 (±1.15)	2.87 (±1.18)	3.08 (±1.07)	0.204
Spirometry				
FEV_1 pp	84.11 (±17.86)	91.63 (±13.15)	69.14 (±16.57)	<0.001
FVC pp	85.11 (±17.76)	91.77 (±13.69)	71.86 (±17.57)	<0.001
FEV_1/FVC	78.64 (±8.76)	79.80 (±5.54)	76.32 (±12.70)	0.016

Abbreviations: BMI = body mass index; BP = blood pressure; FEV_1 = forced expiratory volume in 1 s; FEV_1/FVC = ratio of FEV_1 to FVC; FVC = forced vital capacity; HbA1c = glycated hemoglobin; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; pp = percentage predicted.Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP >/ = 130 mmHg and/or diastolic BP >/ = 80 mmHg. Obesity: BMI≥30 kg/m^2.

[a] Impaired spirometry defined as the presence of pulmonary restriction and/or airway obstruction.

Table 2
Spirometric and 6MWT measures in the study participants.

Characteristics	All Participants	Normal Pulmonary Function	Pulmonary Dysfunction *	*P*-Value
6MWT Distance				
6MWD, m	435.90 (±80.51)	451.70 (±76.91)	404.67 (±78.71)	<0.001
6MWT< 400 m (%)	71 (27.1%)	36 (20.7%)	35 (39.8%)	0.001
Oxygen Saturation				
Pre 6MWT SpO_2 (%)	98.86 (±1.31)	99.01 (±1.15)	98.57 (±1.54)	0.018
Post 6MWT SpO_2 (%)	98.04 (±1.76)	98.17 (±1.70)	97.77 (±1.85)	0.082
ΔSpO_2 (%)	1.84 (±1.49)	1.84 (±1.52)	1.85 (±1.43)	0.946
Lowest SpO_2 (%)	97.00 (±1.76)	97.15 (±1.66)	96.72 (±1.94)	0.060
Heart Rate				
Pre 6MWT HR, bpm	80.68 (±11.89)	81.47 (±12.61)	79.09 (±10.19)	0.125
Post 6MWT HR, bpm	107.29 (±17.77)	107.94 (±19.10)	106.01 (±14.83)	0.370
ΔHR, bpm	26.62 (±15.88)	26.47 (±16.80)	26.92 (±13.98)	0.829
HR_{max}, bpm	117.26 (±18.94)	117.14 (±20.52)	117.50 (±15.45)	0.886
HR_{max} pp	72.07 (±13.14)	71.46 (±14.49)	73.28 (±9.91)	0.289
HR_{max} pp > 80	66 (25.1%)	43 (24.6%)	23 (26.1%)	0.782
Borg Scores				
Pre-Borg Dyspnea Score	0.52 (±0.57)	0.42 (±0.54)	0.73 (±0.58)	<0.001
Post-Borg Dyspnea Score	3.02 (±0.94)	2.92 (±0.77)	3.22 (±1.18)	0.015

Abbreviations: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; bpm = beats per minute; HR = heart rate; max = maximum; pp = percentage predicted; SpO_2 = peripheral capillary oxygen saturation.
Δ = difference between the variable at the start and end of 6MWT
HR_{max} is the maximum HR during the 6MWT. HR_{max} pp is the HR_{max} expressed as a percentage of the age predicted maximum HR (i.e., 220-age). Therefore, HR_{max} pp = 100 * HR_{max}/(220-age).

FEV_1/FVC ratio and impaired exercise capacity. In the unadjusted model, decreasing Z-score FEV_1 [odds ratio 1.40, 95% CI 1.07–1.83, p = 0.013] and Z-score FVC [1.37 (1.06–1.76), 0.016], but not Z-score FEV_1/FVC ratio [1.00 (0.78–1.27), 0.972] were significantly associated with higher odds of impaired exercise capacity. In the fully adjusted model, the strength of association remained statistically significant for Z-score FEV_1 [1.60 (1.06–2.41), 0.025] but not Z-score FVC [1.48 (0.98–2.23), 0.065].

4. Discussions

4.1. Key findings

In this study among adults with T2D without primary heart and lung disease, impaired submaximal exercise capacity was common, with over a quarter (27.1%) of study participants affected. We observed a positive association between impaired pulmonary function and impaired exercise capacity. Decreasing Z-score FEV_1 and FVC but not FEV_1/FVC ratio was associated with impaired exercise capacity. After adjustment for a wide range of conventional risk factors, the strength of association remained statistically significant for Z-score FEV_1 and higher odds of impaired exercise capacity.

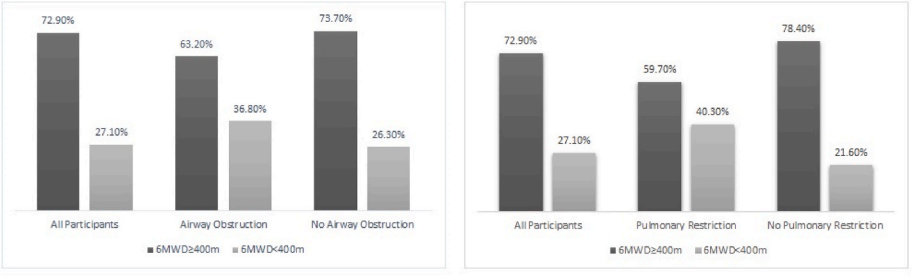
4.2. Discussion of key findings

While the impact of T2D on the lungs has been fairly investigated [7,15,29], important gaps remain on the impact of T2D on exercise capacity. Previous studies assessing exercise capacity (using either CPET or 6MWT) in T2D have focused on individuals with coexisting heart disease including heart failure [30,31]. In these studies, diabetes was reported to be an additional factor that reduces the distance walked irrespective of coexisting heart failure. In their study that included 131 individuals with diabetes without acute or chronic pulmonary disease, Kuziemski et al. [16] reported a reduction in 6MWD in individuals with diabetes compared with their non-diabetes control. In their paper, the

Table 3
Associations between spirometric indices and exercise tolerance.

	Odds ratio (95% confidence interval), p-value	
	Unadjusted Model	Fully Adjusted Model *
Decreasing Z-score FEV_1	1.40 (1.07–1.83), 0.013	1.60 (1.06–2.41), 0.025
Decreasing Z-score FVC	1.37 (1.06–1.76), 0.016	1.48 (0.98–2.23), 0.065
Decreasing Z-score FEV_1/FVC ratio	1.00 (0.78–1.27), 0.972	1.36 (0.93–1.99), 0.113

Definition of abbreviations: FEV_1 = forced expiratory volume in 1 s; FEV_1/FVC = ratio of FEV_1 to FVC; FVC = forced vital capacity; pp = percentage predicted. The fully adjusted model was adjusted for age, sex, diabetes duration, HbA1c, smoking, suboptimum blood pressure control, body mass index, and total cholesterol concentration. Suboptimal blood pressure control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP >/ = 130 mmHg and/or diastolic BP >/ = 80 mmHg.



A B

Fig. 1. Proportion of individuals with 6MWD<400 m in individuals with and without A) Airway obstruction and B) Lung Restriction. Pulmonary restriction is defined as measured forced vital capacity less than the lower limit of normal.
Airway obstruction is defined as measured ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC ratio) less than the lower limit of normal.

authors hypothesized that impaired exercise tolerance is commoner in people with diabetes compared with people without diabetes because of impaired cardiac function in the setting of diabetes and/or diabetes-related cardiac complications including heart failure [16]. A unique contribution of our study to the existing literature is that our study population excluded individuals with primary heart or lung disease, and patients with heart failure, which independently affect exercise capacity. Based on the results of our study, impaired exercise capacity is common in individuals with T2D without primary heart or lung disease, with over a quarter of the study participants affected. Over a quarter of the study population having impaired submaximal exercise capacity (based on reduced 6MWD) is clinically relevant considering its impact on quality of life and activities of daily living [32], as well as its role in predicting mortality [33,34].

The first spirometric index we associated with reduced exercise capacity was FEV_1. In this study, lower FEV_1 was associated with higher odds of impaired exercise capacity. While studies assessing this relationship are lacking in T2D, reports exist in individuals with chronic pulmonary diseases [8,9,35,36]. The result of the current study generally agrees with previous reports in individuals with chronic pulmonary diseases [8,9,35,36]. These correlations suggest that in T2D, lower FEV_1 might play an important role in 6MWT performance. The biological basis of this association is uncertain. First, the observed association could reflect the impact of common risk factors for reduced lung function and exercise tolerance such as COPD or heart failure. However, the study excluded individuals with primary lung disease and/or heart failure. Secondly, the observed asociation may reflect the impact of diabetes-related risk factors like poor glycemic control and increased duration of diabetes on lung function and exercise capacity. However, the associations remained significant after adjusting for these risk factors. Thirdly, it may well be the case that reduced FEV_1 is causally related to impaired exercise capacity via intermediary processes including chronic hypoxia. Fourthly, the relationship could reflect the impact of common cardiovascular, respiratory, and diabetes-related risk factors in pulmonary function and exercise capacity. However, the observed associations remained significant after adjusting for these conventional risk factors. Finally, it is possible that such an association between low FEV_1 and impaired exercise capacity could reflect the impact of T2D on the pulmonary system and systems involved in exercise capacity including the heart, systemic circulation, and peripheral circulation. This cross-sectional design cannot exclude this possibility.

The second spirometric index we associated with reduced exercise capacity was FVC. In an unadjusted model, lower FVC was associated with higher odds of impaired exercise capacity. Our findings agree with previous reports in individuals with chronic pulmonary diseases [8,9,35,36]. Compared with lower FEV_1, the association between FVC and exercise capacity was less robust; unlike FEV_1, the association between lower FVC and impaired exercise capacity was explained by the conventional cardiovascular and pulmonary risk factors. This is in line with the existing evidence that compared with FVC, FEV_1 is a better predictor of cardiovascular events [17–19]. Why FEV_1 is better associated with exercise capacity than FVC is uncertain. It could be because low FEV_1 represents a broader range of pulmonary functional impairments compared with low FVC [27]; FEV_1 may be reduced in both obstructive and restrictive pulmonary defects, while FVC is typically reduced in restrictive pulmonary defects. Besides the broader diagnostic utility, FEV_1 has robust prognostic utility. For example, reduction in FEV_1 is an established marker for disease progression as well as a predictor of mortality [37,38], independent of cardiac function [39]; FEV_1 is shown to be a marker of mortality even in individuals with a mild pulmonary disease [37].

The current study did not find any significant association between lower FEV_1/FVC ratio and impaired exercise capacity in T2D. While there are no studies in T2D to compare with, our findings agree with studies in obstructive lung diseases like COPD [8] and restrictive lung diseases like pulmonary sarcoidosis [35] and cystic fibrosis [9]. While the biological basis of the differential associations of FEV_1 or FVC and FEV_1/FVC with exercise capacity remains unclear, the observation in this study and other studies in individuals with primary lung disease suggest that compared with obstructive airway pattern, restrictive pulmonary patterns better correlate with impaired exercise capacity.

Regardless of the biological basis of the associations observed in this study, spirometry (especially FEV_1) might be an important marker for exercise capacity in individuals with T2D. This study supports the use of FEV_1 in addition to other tools, in assessing the exercise capacity of patients with T2D. Based on the cross-sectional design, arguments can also be made for the utility of 6MWD in assessing the likelihood of reduced FEV1 in individuals with T2D; this may be relevant in regions where spirometry services are not available, and in individuals who cannot perform technically acceptable spirometry.

This study is clinically relevant in a number of ways. First, the study suggests that FEV_1 may be an important marker for assessing exercise capacity in individuals with T2D. This may be important in situations where the 6MWT cannot be performed, including cases where the set-up for conducting the 6MWT is not available, or where 6MWT is contraindicated (e.g. unstable angina or myocardial infarction within the previous month or resting heart rate >120 beats per minute) or systolic BP/Diastolic BP > 180 mm Hg/100 mm Hg) [20]. There are also situations where the 6MWT is not feasible, such as in lower limb amputated patients. Secondly, our findings show that FEV_1 could be considered when recommending exercise programs for patients with T2D. Conversely, individuals with T2D with exercise intolerance may benefit from pulmonary evaluation including periodic evaluation of FEV_1. Finally, our findings suggest that interventions aimed at preventing reductions in FEV_1 in individuals with T2D may be useful in reducing the likelihood of impaired exercise capacity.

4.3. Limitations

Our study has limitations. First, the cross-sectional design limits us from precluding reverse causation (i.e., impaired exercise capacity contributing to reduced pulmonary function dysfunction). Secondly, this study did not assess cardiopulmonary exercise testing (CPET), or alternative testing of impaired exercise capacity which provides additional information including measurement of peak oxygen uptake, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise [20]. However, the 6MWT and CPET measures correlate well. For example, there is a significant correlation ($r = 0.73$) between 6MWD and peak oxygen uptake from CPET [20]. Finally, we used a walking course 20 m in length for the 6MWT; the ATS guidelines recommend a walking course 30 m in length [20]. However, the ATS guidelines do not preclude 20- or 50-m walking courses; a multicenter study which is cited in the ATS guidelines showed that walking course length has no significant effect on walking distance, for straight courses ranging from 50 to 164 ft [20,40].

5. Conclusions

This study assessing the association between measures of spirometry and 6MWT in people with T2D shows a positive association between reduced FEV_1 and impaired exercise capacity, independent of the conventional cardiovascular and pulmonary risk factors. Future studies might look at the longitudinal relationship between FEV_1 and exercise capacity, as well as the potential mechanisms linking low FEV_1 to impaired exercise capacity in T2D. Studies characterizing the optimal exercise levels based on a patient's FEV_1 are also needed.

Authorship

Contributions: All authors have contributed substantially to this article and approved the submission. C.F.H–B conceived the idea. M.F.K,

C·F·H–B, and C.A-B experimented. C.F.H–B, and M.F·K, were responsible for statistical analysis. C.F.H–B, M.F·K, and C.A-B were responsible for data interpretation. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions about the accuracy or integrity of any portion of the work are appropriately investigated and resolved. C.F.H–B. takes responsibility for the fact that this study has been reported honestly, accurately, and transparently, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Funding

This work was funded by the Faculty Development Grant of the University of Ghana College of Health Science.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are very grateful to the study participants for taking part in the study. Patience Vormatu deserves special commendation for coordinating the recruitment and study procedures. We thank the research assistants (Abraham Ablor, Alexander Danquah, Maame Boatemaa Ansong, Michael Adjei, and Nii Adjetey Kwaw Wills) for assisting with interviews and anthropometric measurements. We also Edem Ahiabor for assisting with the retinal photography. We gratefully acknowledge the leadership and staff of the NDMRC for helping with various aspects of the study. We also acknowledge Elikem Jasper Butsey, Faustina Aba Amoah, Odelia Tamakloe, and Seth Agyemang, and the staff of the National Cardiothoracic Centre Laboratory and the KBTH Accident and Emergency Laboratory for running the biochemical tests. We are grateful to Dr. Charles Antwi-Boasiako, Dr. Yvonne Dei-Adomako, and Mr. Enoch Mensah for their support in biobank management and the high-quality storage of collected samples.

References

[1] Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119. https://doi.org/10.1016/j.diabres.2021.109119.
[2] Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26(2):77–82. https://doi.org/10.2337/diaclin.26.2.77.
[3] Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther 2008;88(11):1322–35. https://doi.org/10.2522/ptj.20080008.
[4] Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321(7258):405–12.
[5] Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the diabetes & aging study). Diabetes Care 2019;42(3):416–26. https://doi.org/10.2337/dc17-1144.
[6] Richter EA, Sylow L, Hargreaves M. Interactions between insulin and exercise. Biochem J 2021;478(21):3827–46. https://doi.org/10.1042/BCJ20210185.
[7] Díez-Manglano J, Asìn Samper U. Pulmonary function tests in type 2 diabetes: a meta-analysis. ERJ Open Res 2021;7(1). https://doi.org/10.1183/23120541.00371-2020.
[8] Agrawal MB, Awad NT. Correlation between six minute walk test and spirometry in chronic pulmonary disease. J Clin Diagn Res JCDR 2015;9(8):OC01–4. https://doi.org/10.7860/JCDR/2015/13181.6311.
[9] Roshanzamir Z, Shirzadi R, Modaresi M. The correlation between 6-min walk test and respiratory parameters in children with cystic fibrosis. Ir J Med Sci 2022;191(1):289–94. https://doi.org/10.1007/s11845-021-02564-9.
[10] Santos VMF, Boaventura R, Meira L, et al. Correlation between exercise capacity with FVC%, FEV1% and RV% in patients with airways diseases and severe and very severe lung function obstruction. Eur Respir J 2016;48(suppl 60). https://doi.org/10.1183/13993003.congress-2016.PA2267.
[11] Klinger JR. Group III pulmonary hypertension: pulmonary hypertension associated with lung disease: epidemiology, pathophysiology, and treatments. Cardiol Clin 2016;34(3):413–33. https://doi.org/10.1016/j.ccl.2016.04.003.
[12] McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe M, Ferrucci L. The six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. Circulation 2014;130(1):61–8. https://doi.org/10.1161/CIRCULATIONAHA.114.007002.
[13] Hayfron-Benjamin CF, Amoah AGB, Maitland-van der Zee AH, et al. Associations between macrovascular and renal microvascular dysfunction in type 2 diabetes and non-diabetes. Microvasc Res. Published online 2021;8:104162. https://doi.org/10.1016/j.mvr.2021.104162. March.
[14] Khateeb J, Fuchs E, Khamaisi M. Diabetes and lung disease: a neglected relationship. Rev Diabet Stud RDS 2019;15:1–15. https://doi.org/10.1900/RDS.2019.15.1.
[15] van den Borst B, Gosker HR, Zeegers MP, Schols AMWJ. Pulmonary function in diabetes: a metaanalysis. Chest 2010;138(2):393–406. https://doi.org/10.1378/chest.09-2622.
[16] Kuziemski K, Słomiński W, Jassem E. Impact of diabetes mellitus on functional exercise capacity and pulmonary functions in patients with diabetes and healthy persons. BMC Endocr Disord 2019;19(1):2. https://doi.org/10.1186/s12902-018-0328-1.
[17] Kassim AA, Payne AB, Rodeghier M, Macklin EA, Strunk RC, DeBaun MR. Low forced expiratory volume is associated with earlier death in sickle cell anemia. Blood 2015;126(13):1544–50. https://doi.org/10.1182/blood-2015-05-644435.
[18] Bikov A, Lange P, Anderson JA, et al. FEV1 is a stronger mortality predictor than FVC in patients with moderate COPD and with an increased risk for cardiovascular disease. Int J Chronic Obstr Pulm Dis 2020;15:1135–42. https://doi.org/10.2147/COPD.S242809.
[19] Hayfron-Benjamin CF, Asare EV, Boafor T, et al. Low FEV1 is associated with fetal death in pregnant women with sickle cell disease. Am J Hematol. Published online 2021;13. https://doi.org/10.1002/ajh.26236. May.
[20] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111–7. https://doi.org/10.1164/ajrccm.166.1.at1102.
[21] Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med 2019;200(8):e70–88. https://doi.org/10.1164/rccm.201908-1590ST.
[22] Hayfron-Benjamin CF, Quartey-Papafio TR, Amo-Nyarko T, et al. Relationships of blood pressure and control with microvascular dysfunction in type 2 diabetes. Diabetes Epidemiol Manag. Published online 2023;5:100160. https://doi.org/10.1016/j.deman.2023.100160. July.
[23] Antwi-Boasiako C, Obeng KA, Amissah-Arthur KN, et al. Association between albuminuria and retinal microvascular dysfunction in type 2 diabetes with and without hypertension. Diabetes Epidemiol Manag 2023;11:100139. https://doi.org/10.1016/j.deman.2023.100139.
[24] Whelton PK, Carey RM, Mancia G, Kreutz R, Bundy JD, Williams B. Harmonization of the American College of Cardiology/American heart association and European society of Cardiology/European society of hypertension blood pressure/hypertension guidelines: comparisons, reflections, and recommendations. Eur Heart J 2022;43(35):3302–11. https://doi.org/10.1093/eurheartj/ehac432.
[25] Passarella P, Kiseleva TA, Valeeva FV, Gosmanov AR. Hypertension management in diabetes: 2018 update. Diabetes Spectr 2018;31(3):218–24. https://doi.org/10.2337/ds17-0085.
[26] Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324–43. https://doi.org/10.1183/09031936.00080312.
[27] Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948–68. https://doi.org/10.1183/09031936.05.00035205.
[28] Enright PL. The six-minute walk test. Respir Care 2003;48(8):783–5.
[29] Saini M, Kulandaivelan S, Bansal VK, et al. Pulmonary pathology among patients with type 2 diabetes mellitus: an updated systematic Review and meta-analysis. Curr Diabetes Rev 2020;16(7):759–69. https://doi.org/10.2174/1573399815666190716130324.
[30] Abe T, Yokota T, Fukushima A, et al. Type 2 diabetes is an independent predictor of lowered peak aerobic capacity in heart failure patients with non-reduced or reduced left ventricular ejection fraction. Cardiovasc Diabetol 2020;19:142. https://doi.org/10.1186/s12933-020-01114-4.
[31] Ingle L, Reddy P, Clark AL, Cleland JGF. Diabetes lowers six-minute walk test performance in heart failure. J Am Coll Cardiol 2006;47(9):1909–10. https://doi.org/10.1016/j.jacc.2006.02.005.
[32] Tekerlek H, Cakmak A, Calik-Kutukcu E, et al. Exercise capacity and activities of daily living are related in patients with chronic obstructive pulmonary disease. Arch Bronconeumol 2020;56(4):208–13. https://doi.org/10.1016/j.arbres.2019.06.015.
[33] Karanth MS, Awad NT. Six minute walk test: a tool for predicting mortality in chronic pulmonary diseases. J Clin Diagn Res JCDR 2017;11(4):OC34–8. https://doi.org/10.7860/JCDR/2017/24707.9723.
[34] Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J 2009;39(8):495–501. https://doi.org/10.1111/j.1445-5994.2008.01880.x.
[35] Alhamad EH. The six-minute walk test in patients with pulmonary sarcoidosis. Ann Thorac Med 2009;4(2):60–4. https://doi.org/10.4103/1817-1737.49414.

[36] Ameri HFA. Six minute walk test in respiratory diseases: a university hospital experience. Ann Thorac Med 2006;1(1):16. https://doi.org/10.4103/1817-1737.25865.
[37] Duong M, Islam S, Rangarajan S, et al. Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV1 (PURE): an international, community-based cohort study. Lancet Global Health 2019;7(5):e613–23. https://doi.org/10.1016/S2214-109X(19)30070-1.
[38] Szczesniak R, Heltshe SL, Stanojevic S, Mayer-Hamblett N. Use of FEV1 in cystic fibrosis epidemiologic studies and clinical trials: a statistical perspective for the clinical researcher. J Cyst Fibros Off J Eur Cyst Fibros Soc 2017;16(3):318–26. https://doi.org/10.1016/j.jcf.2017.01.002.
[39] Magnussen C, Ojeda FM, Rzayeva N, et al. FEV1 and FVC predict all-cause mortality independent of cardiac function - results from the population-based Gutenberg Health Study. Int J Cardiol 2017;234:64–8. https://doi.org/10.1016/j.ijcard.2017.02.012.
[40] Sciurba F, Criner GJ, Lee SM, et al. Six-minute walk distance in chronic obstructive pulmonary disease: reproducibility and effect of walking course layout and length. Am J Respir Crit Care Med 2003;167(11):1522–7. https://doi.org/10.1164/rccm.200203-166OC.