Restrictive pulmonary deficit is associated with inflammation in sub-optimally controlled obese diabetics

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ABSTRACT Caribbean data linking inflammation, pulmonary dysfunction and diabetes is unavailable. Spirometry, acanthosis nigricans, hs-CRP were assessed in 109 type 2 diabetics (43% males) mean age =55.6 years, BMI =29.29 kg/m^2, waist circumference =103.86 cm. Residual FEV1/FVC increased with age (P=0.005), BMI (P=0.011) and waist circumference (P=0.003). Residual FVC related inversely to hs-CRP (–0.178), P<0.06) systolic (–0.028, P<0.031), diastolic (–0.247, P<0.010) pressure and weight (–0.25, P<0.009). Residual FEV1 related inversely to diastolic pressure (–0.219, P<0.023), hs-CRP (–0.234, P<0.015), acanthosis nigricans (–0.029, P<0.029). HbA1C and residual FEV1 predict high hs-CRP (P=0.011, P=0.046). Low FVC with inflammation presents in poorly controlled obese diabetics.

KEY WORDS Impaired pulmonary function; systemic inflammation; diabetes mellitus type 2; obesity

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Introduction

A growing body of evidence links low-grade systemic inflammation with the metabolic syndrome, diabetes mellitus and reduced pulmonary function. Among the multiple factors that appear to be associated with diabetes mellitus, studies suggest abnormal lung function is present in individuals with diabetes (1,2). A three year follow-up of The Atherosclerosis Risk in Communities (ARIC) Study (3), demonstrated that the reduction in forced vital capacity (FVC) was swifter in diabetic adults than in their non-diabetic counterparts. The rate of decline was related to the severity of diabetes, lending sound support to the hypothesis that the lung is a target organ for injury from diabetic disease.

The NHANES Study revealed the prevalence of diabetes mellitus and the metabolic syndrome significantly increased as the predicted FVC decreased and every 10% reduction in FVC was associated with 77% higher mortality in people with the metabolic syndrome (4). Systemic inflammation in these patients, estimated by C-reactive protein (CRP) was inversely related to FVC (5). In another report (6) on 9,500 apparently healthy non-smoking Korean males, those in the lowest FVC or FEV1 quartile had the highest hs-CRP (high sensitivity-CRP) levels. The metabolic syndrome, insulin resistance and systemic inflammation were important risk factors for reduced lung function in this study. Dahl *et al.* (7) measured serum CRP in subjects with airway obstruction and found that hospitalization or death due to chronic obstructive pulmonary disease (COPD) were both increased in subjects with increased baseline serum CRP levels. In patients with declining FEV1 and airways obstruction, serum CRP was also a stronger and independent predictor of COPD mortality than of COPD hospitalization. Collectively, these studies suggest CRP is a surrogate marker of lung injury in the chronic diseases studied. Such relationships have not been explored in the West Indian populace, which is afflicted with high prevalence and morbidity of diabetes. In our earlier studies we found that forced expiratory volume (FEV1) (8) was reduced in in-patients with vascular disease, an important outcome measure in diabetics, and observed a similar relationship for FVC in outpatients attending chronic disease clinics in Trinidad (9).

In countries of the Caribbean Community Market (CARICOM) the age adjusted death rate for diabetes in 2000 was >100 per 100,000, compared with less than 20 per 100,000 from Canada and the USA. Across the Caribbean, the overall prevalence of diabetes mellitus is estimated at

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about 9% (10) and in Trinidad and Tobago, it is 12.7% (11). Trinidad and Tobago, where life style and socio-economic changes have transformed the health profile of the population, portrays a model of the climbing health threat, prevalence and societal burden of NIDDM for the Caribbean (12,13). The interrelationship between pulmonary involvement and low grade inflammation studied elsewhere (14,15), has not been examined in the Caribbean where diabetes presents a significant health burden. We cross-sectionally examined the relationship between systemic inflammation, evaluated by hs-CRP, lung function and type 2 diabetes in Trinidad.

Methods and subjects

The Ethics Committee of The University of The West Indies (St. Augustine) approved the study, and participants gave written, informed consent.

This was a cross sectional study in 109 known adult diabetics attending two endocrinology clinics in north-central Trinidad. These clinics receive patient referrals from all over the island and even from Tobago, the sister isle, for specialist attention to control diabetes or arrest its complications. Patients were recruited as they presented to the clinics.

Adult (>17 years) type 2 diabetic patients of both genders were invited to participate. A diabetic patient was defined as one whose fasting plasma glucose was >126 mg/dL, attending a Diabetic Clinic and receiving prescribed treatment for the condition. Patients were evaluated for the presence of the Metabolic Syndrome using criteria of the International Diabetes Federation (16). Patients who were receiving exogenous corticosteroids, including inhaled steroids or those in whom spirometry could not be performed using ATS criteria (17) were excluded.

On Encounter 1, subjects were interviewed to document demography, family and smoking history, and examined for anthropometric measurements using a stadiometer and calibrated weights, waist circumference (midway between the lower rib margin and iliac crest), BMI and blood pressure. Blood was collected for estimation of hs-CRP, lipid profile, HbA1c, and uric acid. All biochemical tests (including crp) were conducted with the Vitros 250 Clinical Chemistry Analyzer (Johnson & Johnson Vitros 250, Ortho-Clinical Diagnostics Inc., Rochester NY 14626, USA), with the appropriate quality controls. Analysis of CRP was done using dry chemistry kits with a detection limit of 0.70 mg/dL. Subjects were examined for acanthosis nigricans, a surrogate marker of hyper-insulinemia, which was graded for severity on the neck using the scale described by Burke *et al.* (18).

On Encounter 2, one week later, lung function was assessed 20 minutes after inhaling 200 μgm salbutamol, following the ATS criteria for methodology and equipment (17). Responses from at least three technically satisfactory curves from three acceptable blows were considered. A post-bronchodilator FEV_1/FVC <0.7 informed on the diagnosis of obstructive lung disease and less than 80% predicted FVC was indicative of a restrictive ventilatory defect. Post-bronchodilator spirometric indices were assessed according to the guidelines of the American Thoracic Society by open-circuit testing. Data included in the analysis satisfied the parameters of acceptability and reproducibility (17) and predicted values were calculated using Hankinson equations (19).

Using the method described by Brown *et al.* (20), steroid sensitivity of the skin was assayed on this occasion with beclomethasone dipropionate dissolved in 95% ethanol (1,000 μgm/mL); 95% ethanol was the control. Test or control (10 μL) solutions were randomly applied to two test sites on the flexor aspect of the middle third of the forearm, in 2 cm diameter markings cut on double-sided adhesive tape. After complete drying, the site was occluded with 'Saran' wrap for sixteen hours. Two trained 'blinded' observers examined both sites for blanching under fluorescent light and the average reading was considered. Gradation of blanching was scored on a 5 point scale from 0-4, for normal skin/no blanching, faint, obvious, intense, and intense blanching beyond the circumscribed test area respectively. The absence of a blanching response after steroid application indicates an inflammatory state is present, obliterating the topical pharmacodynamic steroid effect, resulting in cutaneous steroid insensitivity.

Stastical analysis

Data was analysed using SPSS version 12. Data for continuous variables were expressed as means [standard deviation (SD); Standard Error (SE) or 95% Confidence Interval (95% CI)] and discrete data were summarized as number (%). Associations were considered statistically significant at the 5% level. For purposes of analysis acanthosis nigricans was binary coded as 0 or one *vs.* two to four. Skin vasoconstrictor assay was binary coded to no response *vs.* any response.

Residual pulmonary function was determined by subtracting the predicted from the measured value; negative values thus reflect pulmonary function less than expected as suggested in the Framingham Study (2). Univariate relationships with residual lung function measures were examined by Pearson's correlation.

A generalized univariate linear model was constructed with hsCRP as outcome variable. All variables having significant univariate relationship with hsCRP were included in the model. Though gender was related to some of the baseline variables it was not related to hs-CRP and its inclusion in the multivariate model with hs-CRP as outcome variables did not change the outcome and so we show the data without inclusion of gender in the model. Acanthosis nigricans and skin vasoconstrictor response were included in the model as fixed factors, all other independent variables were included as covariates. The model test of significance was P=0.002.

Table 1. Demographic and Social characteristics of patients in this study.

Parameter	Gender	n	Mean (SD)
Age (years)	Male	47	56.96 (11.04)
	Female	62	54.60 (11.34)
Weight (kg)	Male	47	83.77 (22.45)
	Female	62	77.75 (18.49)
Waist circumference (cm)	Male	47	99.05 (12.95)**
	Female	62	107.51 (19.58)
BMI ($kg \cdot m^{-2}$)	Male	47	28.34 (7.05)
	Female	62	30.02 (6.24)
Hip circumference	Male	47	99.71 (10.67)**
	Female	62	106.58 (13.32)
Ankle circumference	Male	47	22.20 (1.94)
	Female	61	21.34 (2.36)
N (%)			
		Male	Female
Ethnicity			
Afros (n=32)		12 (25.5)	20 (32.3)
Indos (n=67)		32 (68.1)	35 (56.5)
Other (n=10)		3 (6.4)	7 (11.3)
Highest level of education attained			
Primary		16 (34.0)	23 (37.1)
Secondary		23 (48.9)	26 (41.9)
Tertiary		7 (11.0)	14.9 (17.7)
Smoking history			
Never smoked		22 (46.8)	54 (87.1)***
Current and Ex-smokers		25 (53.2)	8 (12.9)***
Alcohol intake			
Never		44 (93.6)	61 (98.4)
Physical exercise			
Regular exercise		27 (58.7)	38 (61.3)

**P<0.01, ***P<0.001.

Results

Sample description

Two of the 109 subjects who gave written consent for the study, could not do the skin vasoconstrictor assay, thus analyses for this assay are for 107 patients. The majority (61.5%) of subjects were of African descent. The mean (SD) age of the population was 55.6 (11.2) years and comprised 56.88% women (Table 1).About one third (33%) of subjects were ex- or current smokers. The mean BMI (29.29 kilogram/m^2) and waist circumference (103.86 cm) were high in the sample studied. The mean systolic and diastolic blood pressures were within the normal range as were mean lipid and mean uric acid levels (Table 2). Based on the IDF criteria (16) of HbA1c ≤6.5, glucose control was sub-optimal in 63.9% of subjects (Figure 1); HbA1c was greater than 8% in 25 percent of patients. In 25% of subjects the hs-CRP was greater than 5 mg/L.

Using the IDF Criteria 104 (95.4%) patients had central obesity, 61 (55.96%) had hypertension, 28 (25.4%) had high serum triglyceride levels and 61 (56%) had low HDL and 83.5% of subjects (n=91) suffered with the metabolic syndrome. Half the sample (50.05%) exhibited grade two-four acanthosis nigricans and 55% of subjects failed to respond to the skin vasoconstrictor assay (Table 2).

Social factors

Only 16.5% of the sample had tertiary education and only 13.7% had an annual income exceeding 10, 000 TT dollars (about $1587

Table 2. Physiologic and Biochemical Indices in diabetic subjects.

Parameter	Gender	N	Mean (SD)
BP systolic (mmHg)	Male	46	127.24 (20.59)
	Female	62	121.94 (17.82)
BP diastolic (mmHg)	Male	46	76.52 (11.41)
	Female	62	73.85 (11.31)
Cholesterol total (mg/dL)	Male	47	150.47 (39.58)***
	Female	61	191.10 (36.12)
Cholesterol LDL (mg/dL)	Male	47	85.30 (33.89)***
	Female	61	117.56 (33.30)
Cholesterol HDL (mg/dL)	Male	47	44.21 (20.94)
	Female	61	52.48 (29.30)
Duration of elevated cholesterol, years	Male	46	2.04 (2.59)
	Female	62	3.20 (4.74)
Triglycerides (mg/dL)	Male	47	122.13 (69.18)
	Female	61	122.18 (64.84)
$HbA1_c$	Male	47	6.76 (1.91)*
	Female	61	7.47 (1.75)
hsCRP (mg/L)	Male	47	4.31 (6.38)
	Female	61	4.97 (7.41)
Uric acid (mg/dL)	Male	47	6.91 (2.10)*
	Female	61	5.11 (1.25)
FEV1, PostBD (L)	Male	47	2.51 (0.51)***
	Female	62	1.91 (0.37)
FVC, Post BD (L)	Male	47	3.01 (0.57)***
	Female	62	2.21 (0.43)
FEV1/FVC %	Male	47	83.34 (5.54)***
	Female	62	86.49 (4.31)
FEV1 reversibility	Male	47	2.54 (5.41)
	Female	62	1.72 (5.23)
FEV1 % predicted	Male	47	87.08 (16.98)
	Female	62	89.46 (14.08)
FVC % predicted	Male	47	81.71 (14.47)
	Female	62	82.65 (13.18)
Residual FEV1 (L)	Male	47	–0.39 (0.52)
	Female	62	–0.24 (0.30)
Residual FVC (L)	Male	47	–0.69 (0.57)
	Female	62	–0.47 (0.36)

N (%)		
	Male	Female
Acanthosis nigricans (AN)		
AN Neck Grade 0,1 (n=54)	22 (46.8)	32 (51.6)
AN Neck Grade 2-4 (n=55)	25 (53.2)	30 (48.4)
Skin vasoconstrictor assay (n=107)		
=0 (Negative)	29 (61.7)	31 (51.7)
>0 (Positive)	18 (38.3)	29 (48.3)

*P<0.05, **P<0.01, ***P<0.001.

USD). Most patients were non-smokers and denied alcohol consumption. A fairly large subset (39.4%) did not exercise daily or did so irregularly. Patients with a lower annual income were more likely to be smokers (P=0.023). Smokers were more likely to be male and have a lower level of education and lower hip circumference (P<0.05 in all cases). Patients who exercised daily

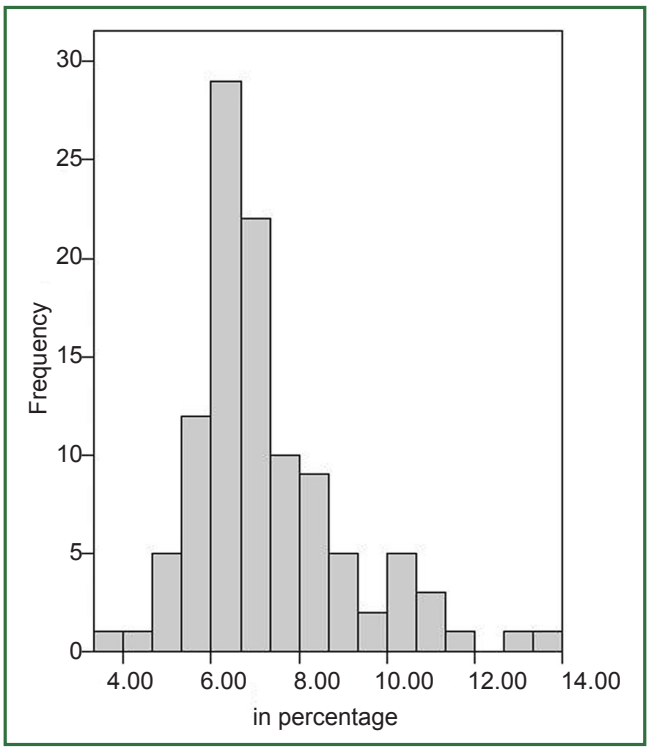

Figure 1. Histogram of HBA1c levels in 109 diabetic patients, Mean (SD) 7.18 (1.86) %.

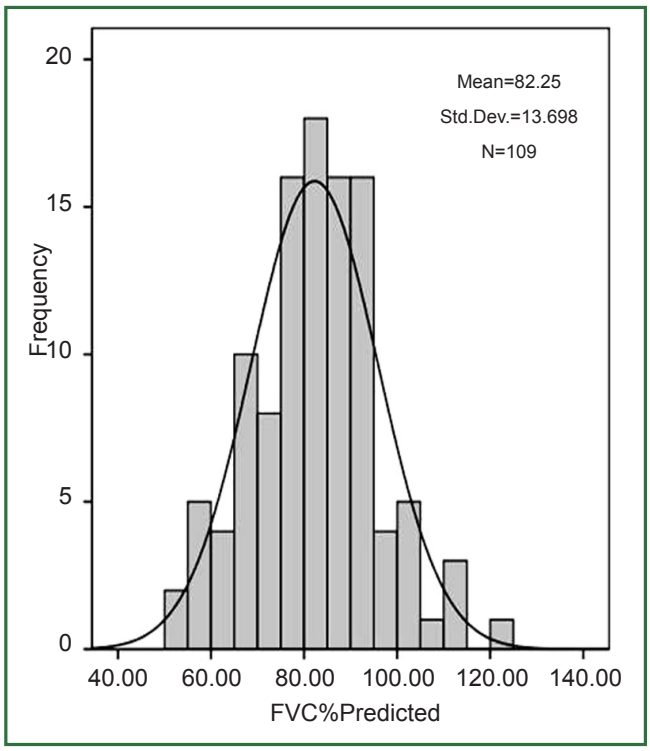

Figure 2. The distribution of FVC expressed as a percent of predicted for age, height and gender for the 109 patients in the study. The histogram shows that 41.3% of subjects had a FVC of less than 80% predicted.

were less likely to report alcohol drinking (P=0.012) and have a family history of cancer (P=0.018).

Lung function

The mean post bronchodilator FVC was 2.56L and mean (SD) FEV1/FVC % was 85.13 (5.10). In 41.3% of subjects the post bronchodilator FVC was less than 80% predicted, and in 6.4% of subjects the FVC was less than 60% (Figure 2).

Lung function and inflammation

Table 3 shows the correlates of lung function and acanthosis with inflammation and variables of the metabolic syndrome. Diastolic blood pressure and hs-CRP were both inversely related to residual FEV1. Though acanthosis nigricans was related to both residual FEV1 and residual FVC, a generalized multivariate linear modeling with residual FEV1 and residual FVC as outcome variables did not elicit a statistically significant relationship with acanthosis nigricans or the skin vasoconstrictor assay. Higher levels of residual FVC were related to lower hs-CRP, and also to lower systolic and diastolic BP, lower serum uric acid and weight. The residual FEV1 value showed a similar relationship to lower hs-CRP and lower diastolic blood pressure. The FEV1/FVC ratio was higher with older age, greater BMI, greater waist circumference and longer history of hypercholesterolaemia.

The inverse relationship of hs-CRP with post-bronchodilator residual bronchodilator FEV1 in Figure 3 draws attention to poor lung function in the presence of systemic inflammation. The high hs-CRP was associated with low residual FEV1 (Figure 3) and a tendency toward a lower residual FVC. Reduced lung function consequent to inflammation in diabetic patients was also demonstrated by the inverse association between acanthosis nigricans and residual post bronchodilator FVC (P=0.048). The systemic inflammation in patients evidenced by an absent vasoconstrictor response to topical steroid correlated negatively with acanthosis nigricans (rho=–0.515, P<0.001).

In Table 4 the generalized linear univariate model with hs-CRP as outcome variable shows that hs-CRP was significantly related to residual FEV1 and HbA1C. The adjusted grand mean hs-CRP for the patients in this study was 4.19 (95% CI: 2.72 to 5.67) mg/L. Based on these data, high HbA1C and low residual FEV1 are predictors of elevated hs-CRP in diabetic patients. Only those variables which had a significant univariate relationship to hs-CRP were included in the multivariate analysis.

Table 3. Pearson's correlates of significance between variables of lung function and inflammation.

Primary variable	Secondary variable	Correlation	P
Acanthosis nigricans	Skin vasoconstrictor assay	–0.515	<0.001
Residual FEV1	Diastolic BP	–0.219	0.023
	Acanthosis nigricans	–0.209	0.029
	hsCRP	–0.234	0.015
Residual FVC	Acanthosis nigricans	–0.220	0.022
	hsCRP	–0.178	0.066
	Systolic BP	–0.208	0.031
	Diastolic BP	–0.247	0.010
	Serum uric acid	–0.20	0.038
	Weight	–0.25	0.009
Residual FEV1/FVC	Age	0.265	0.005
	BMI	0.242	0.011
	Waist circumference	0.285	0.003
	Duration of elevated cholesterol	0.202	0.036
hsCRP	Age	–0.263	0.006
	Acanthosis nigricans	0.209	0.030
	Ankle circumference	0.237	0.014
	BMI	0.201	0.037
	HbA1c	0.254	0.008
	Hip dircumference	0.202	0.036
	LDL dholesterol	0.231	0.016
	Skin vasoconstrictor response	–0.259	0.007

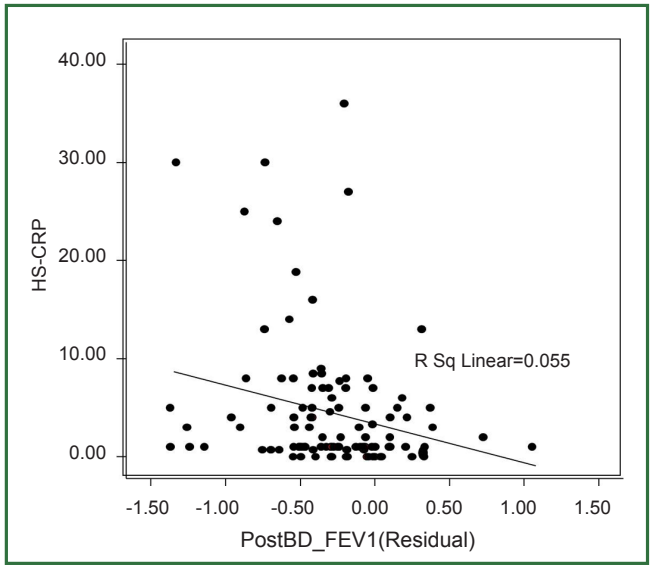

Figure 3. Relation between inflammatory marker (hsCRP) and post-bronchodilator lung function (FEV1) in diabetics with the metabolic syndrome.

Discussion

In this cross sectional study in 109 Type 2 diabetic adults with central obesity, the first West Indian report that looks at pulmonary function in diabetics, we found that 83.5% of subjects had the metabolic syndrome. The Caribbean countries are populated by an integration of peoples drawn from the Indian subcontinent, West Africa, and China, and this populace mix is now seen in diasporas internationally. Despite the high prevalence of diabetes in the Caribbean community, to our knowledge its association with pulmonary function has not been studied in this region.

A restrictive ventilatory defect was observed in 41.3% of subjects in whom postbronchodilator FVC was <80% predicted. Residual FVC was negatively related to hs-CRP, systolic and diastolic BP, and weight and residual FEV1 showed a similar relationship to hs-CRP and diastolic blood pressure. Residual FEV1 and HbA1C were significantly related to hs-CRP and acanthosis nigricans was negatively correlated with skin vasoconstriction. The findings suggest that obese diabetic patients in Trinidad have low-grade systemic inflammation which is associated with restrictive pulmonary disease.

Table 4. Generalized linear univariate model with hsCRP as outcome variable. Only parameter estimates with P-value less than or equal to 0.05 are shown.

Parameter	Estimate	SE	P	95% confidence interval	
Residual FEV1	–9.62	4.76	0.046	–19.06	–0.172
HbA1c	0.90	0.35	0.011	0.208	1.60
Intercept	–22.45	9.50	0.020	–41.30	–3.59

SE = Standard error of the mean.

Lifestyle changes, sedentary work patterns, coincident increases in dietary, alcohol, and tobacco indiscretions influence the onset of the metabolic syndrome, which is demonstrated by the combined associated presence of hyperinsulinemia, obesity and hypertension. Lower income and educational level in the subjects under study was more likely to be associated with smokers, a pattern observed in a world health survey of social determinants of smoking in 48 low-income and middle-income countries (21). The population in this study was treatment responsive for dysplipidemia, hyperuricemia and hypertension, but exhibited high BMI, an excess visceral adipose tissue compartment (increased waist circumference is the clinical correlate) and dysglycemia, all of which encourage insulin resistance and fuels an underlying state of systemic inflammation (22). Guided by earlier reports (23,24) of an absent or markedly diminished response of skin vasoconstriction to a topical glucocorticosteroid we used a failed skin vasoconstriction response as a surrogate non-invasive marker of systemic inflammation secondary to insulin resistance. Our earlier findings in West Indian diabetics established that inflammation (demonstrated by hs-CRP) was associated with high grade acanthosis nigricans (25). This report also showed that high grade acanthosis nigricans was inversely related to a low grade skin vasoconstrictor response supporting the current findings of insensitive steroid induced cutaneous vasoconstriction. The failure of skin blanching presents evidence of an underlying inflammatory state associated with glucocorticoid resistance which could have either provoked it or been derived from it. The high waist circumference and BMI (representative of body fat) is indicative of insulin resistance (26), and points to the co-existent glucocorticoid and insulin resistance as concurrent metabolic co-morbidities.

Diabetics in our study were obese with sub-optimal glucose control and had low predictive FVC which was inversely related to acanthosis nigricans, the surrogate marker of insulin resistance From the inverse relationship of post bronchodilator residual FEV1 with hs-CRP, systemic inflammation is associated with abnormal pulmonary function in obese diabetic patients. Assays of hs-CRP establish it is a robust marker demonstrating the temporal relation between lung function decline and systemic inflammation (15,27). Dennis *et al.* (28) showed mean residual FEV1 and FVC values were lower, FEV1/FVC ratios were higher and inflammatory markers were significantly increased in diabetics without adequate control when compared with those who were well controlled. This report together with the data of Ford and Mannino (1) and the report by Yeh *et al.* (3), strengthens our findings that poorly controlled diabetics have a restrictive lung disorder. The mean FEV1/FVC% and mean FVC% were well below the predicted values and consistent with a restrictive ventilatory defect. In a prospective study by Wannamethee and colleagues (29) of 4,434 British men, lung function was significantly and inversely associated with C-reactive protein and interleukin-6. These authors reported an association between restrictive impaired lung function with incident type 2 diabetes, and partially attributed these findings to metabolic risk factors and inflammation. Chronic hyperglycemia promotes the formation of oxygen radicals which impair pulmonary microvasculature, alveolar epithelial basal lamina and capillary membranes (30). These inflammatory mediators potentially provoke ensuing systemic inflammation in diabetic patients who are in an altered metabolic state (31). We propose that low-grade systemic inflammation evidenced by high hs-CRP links restrictive lung function and obesity in diabetic patients who do not have optimal disease control.

Low FVC and FEV_1 measures have been reported in adult diabetics (32) and in comparison with their non-diabetic counterparts (8). However we did not study non-diabetics. Further study of lung function in well controlled diabetics and those with inefficient glycemic control may inform on the role of hyperglycemia accelerating inflammation and declining lung function, a hypothesis which is supported by our results.

Spirometric impairment of lung function is more common in the general US population after the age of 55 (19). In our study, diabetic patients with impaired FEV1 and FVC had a mean age of 55 years, suggesting abnormal spirometry was present in this population for some time prior to the age of 55 years. Yeh *et al.* demonstrated the decline in FVC is accelerated in diabetes (3) and the rate of annual decline is directly proportional to the severity of glycemia. Restriction of vital capacity is clinically significant when gaseous exchange is impaired (32) and spirometry addresses only partly the ventilatory restriction, without probing into cardiopulmonary dynamics such as alveolar gas exchange. It is therefore necessary to examine components of vital capacity and chest wall–lung mechanics in the diabetic patient without and

particularly with obesity. We recommend obese diabetic patients, be evaluated annually for abnormalities of pulmonary function, with the same focused attention as for dyslipidemia, hypertension, hyperuricemia and renal function. Based on the findings we suggest that diabetic patients with restrictive pulmonary function undergo annual radiological evaluation to detect or exclude an underlying pulmonary parenchymal pathology, an assessment which is planned for our future studies. When cohorts of diabetic and non-diabetic men were examined in a longitudinal study, Litonjua *et al*. (33) found that those predisposed to develop diabetes had reduced lung function several years before diagnosis as compared to men who did not develop diabetes, and the decline in lung function persisted after diabetes developed. This finding taken together with those from the Atherosclerosis Risk in Communities (ARIC) Study (34) demonstrates diminished lung function is an independent predictor of incident type 2 diabetes, pointing to the lung as a target organ of diabetes-induced injury.

In the present study blinded skin vasoconstrictor testing was done in duplicate, a trained researcher did the spirometry evaluation and in the analysis we adjusted for waist circumference and BMI considering the strong relationship between type 2 diabetes and central adiposity. Limitations however are present. This was an open study in a conveniently sampled population and its sensitivity could have been enhanced by a case controlled design between sub-optimally and well controlled diabetics. Only one measurement of HbA1C was done to ascertain glycemic control restricting its usefulness in labeling disease control.

In summary lung function is impaired and associated with inflammation in obese West Indian adult diabetics with inefficient glycaemic control. Physicians should be alerted to evaluating pulmonary function in diabetic patients, and particularly monitor the obese diabetic. These findings are of significant clinical import, for the Caribbean peoples and West Indian migrations globally.

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