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Original Article

Elevated surfactant protein A (SP-A) and reduced lung function status in poorly-controlled diabetes mellitus (DM) subjects

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Abstract

This study assessed lung function status of DM subjects. Materials and methods: 64 females consisting of 32 control and 32 DM subjects participated in this study. Spirometry and blood analysis were used to assess lung function status. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), percentage of forced expiratory volume in one second (FEV_1%), oxygen saturation (SPO_2), fasting blood sugar (FBS), glycaeted haemoglobin (HbA1c), oxygen content of blood (O_2), haemoglobin concentration (Hb) and SP-A were measured. Results: Results obtained showed that the mean FEV_1 and FEV_1% were significantly decreased ($P<0.05$) in DM subjects when compared to control. However, the mean FEV_1% of DM subjects was not significantly below 80%. SPO_2, O_2 content and Hb concentration were significantly reduced ($P<0.05$) in DM subjects when compared to control. BHBA, HbA1c, SP-A were all significantly higher ($P<0.05$) in DM subjects when compared to control. Most DM subjects were poorly controlled as seen in their HbA1c values above 6.8%. The results of this study strongly indicate that poorly controlled DM patients are at risk of restrictive lung disease. There is therefore the need for regular monitoring of lung function status of diabetic patients, especially the poorly controlled.

Keywords: surfactant protein A, spirometry, restrictive lung disease, oxygen saturation, glycaeted haemoglobin, diabetes mellitus

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder usually accompanied by a lot of incapacitating health problems, especially when it is not adequately managed. In 2019, about 463 million adults were estimated to live with DM by the International Diabetes Federation (IDF) worldwide [1]. This value was projected to increase to about 800 million by 2045 [1]. 79% of those with DM live in low- and middle-income countries [2]. The prevalence of type 2 DM in Nigeria is reported at about 7.0% which is doubled the prevalence rate reported by IDF in 2019 which was estimated at about 3.7% [2]. These surge in the prevalence of DM with its multi-organ complications is of serious concern, especially in poorly-controlled DM patients. Poorly managed DM is associated with debilitating multi-organ complications which may be acute or chronic. One of such acute complications of DM include diabetic ketoacidosis (DKA) or non-ketotic hyperosmolar coma with respiratory upset such as Kussmaul breathing. The acute complications of DM are usually medical emergencies and could be fatal if medical response is delayed [3].

The chronic hyperglycaemia associated with DM, especially in poorly-controlled patients, results in the glycosylation of serum and tissue proteins as well as the formation of advanced glycosylation end products. Following their deposition within tissues, glycosylated proteins have pro-inflammatory effects leading to microangiopathic complications such as glomerular hypertrophy and nephropathy as well as proliferation of retinal endothelial cells and retinopathy [4, 5]. Chronic hyperglycaemia causes non-enzymatic glycosylation of proteins such as collagen and elastin causing thickening of basement membrane and microangiopathy [6, 7].

The alveolar capillary network in the lungs is a large microvascular unit and may be affected by DM associated microangiopathy with possible lung dysfunction. More so, diabetic ketoacidosis (DKA), an acute complication of DM has been known to cause a rapid and laboured breathing called kussmaul breathing as a result of abnormally high build-up of ketone bodies, decrease in blood pH, changes in electrolytes and other related substances as a consequence of insulin deficiency and hyperglycaemia [8, 9]. These fluctuations in ketone bodies and associated generation of free radicals common in DM may pose inflammatory consequences in pulmonary tissues.

Despite various reported multi-organ complications associated with DM, pulmonary complications of DM have been poorly characterized. There have been conflicting reports on pulmonary function of diabetic patients. Ehrlich reported normal pulmonary function in DM patients and even concluded that spirometry is not at all necessary for diabetic patients [10]. Meanwhile, a few cohort studies have reported significant decrease in some lung function indices of diabetic patients when compared with apparently healthy subjects [11] but without any pathophysiological mechanism to explain the decrease.

In view of these, there is a need, not just to assess lung function of DM patients but also attempt to establish possible pathophysiological mechanism(s) by assessing some relaparameters which could explain such pulmonary dysfunction (if any), hence this study.

Material and methods

Study area and selection of subjects

The study area was the University of Calabar Teaching Hospital (UCTH). UCTH is a teaching hospital located in Cross River State, Nigeria. DM Subjects were recruited from the diabetic clinic of UCTH while control subjects were apparently healthy doctors and nurses in UCTH. All subjects for this study met inclusion criteria before being recruited into the study.

Sample size and research design

The sample size was calculated using the mean and standard deviation of FEV_1 values for both diabetic and non-diabetic subjects from a previous study (Table 1) [11]. The sample size was calculated using a power of 95 percent and a confidence interval of 95 percent. Using the information in Table 1, the sample size was calculated mathematically using the formular below:

$$n = \frac{(\sigma 1^2 + \sigma 2^2)(Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2}{\Delta^2}$$

where, n = Sample size; σ1 = Standard deviation of group1; σ2 = Standard deviation of group 2; Δ = Differences in group means; Z1-α/2 = Two sided Z value (Z=1.96 for 95% confidence interval); Z1-β = Power (Z1-β for 95% = 1.645)

Participant eligibility criteria

Participants eligible for inclusion in this study were individuals who provided voluntary written informed consent, were non-smokers, and had no evidence of cardiopulmonary dysfunction. Exclusion criteria included the presence of cardiopulmonary dysfunction, current smoking or a past history of cardiopulmonary disease, and unwillingness to participate in the study.

Table 1: Mean, standard deviation and sample size from a previous study.

FEV1	Diabetic	Non-diabetic
Mean	1.9	2.4
Standard deviation	0.6	0.5
Sample size	30	30

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Measurement of FVC, FEV_1, FEV_1% and PEFR

FVC, FEV_1 and FEV_1% were measured using Schiller spirovit SP-1 Spirometer (From Schiller Healthcare, Mumbai, India). All tests were conducted according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines in a quiet room in sitting position after the procedure was carefully demonstrated to the subjects. Each subject was asked to sit on a straight back chair and breathe in as deeply as possible, after which a disposable mouth piece was inserted into the mouth with the lips firmly around the disposable mouth piece; the subject was then asked to breathe out quickly and forcefully into the spirometer. Each subject was made to perform the procedure three times with a minute rest in between trials after which the best of the three readings was recorded.

Measurement of oxygen saturation

Oxygen saturation was measured using pulse oximeter. A wet swab (cotton wool soaked in methylated spirit) was used to clean the index finger of each subject, after which the palmar surface of the index finger was placed on the sensitive spot of the pulse oximeter which measured oxygen saturation.

Measurement of oxygen content of blood

Oxygen content of blood was calculated mathematically using the formular thus: O_2 content = (O_2 binding capacity) × % O_2 saturation + Dissolved O_2 (0.003 × PO_2 which could be negligible), recalling that O_2 binding capacity = 1.34 × Hb concentration [12].

Measurement of some anthropometric parameters

Body weights of subjects were measured using a weighing scale (Hanson, CHINA). Subjects were made to stand upright on the scale after taking off their shoes and stocks and the body weight was read from the weighing scale. Standing height of each subject was taken while the subject stood erect against a height measurement metre rule placed against a wall. The subject's occiput, shoulders, buttocks and back of the heel was made to touch the wall with the subject looking forward. Chest circumference was measured with a measuring tape. This was placed around the chest region and the reading taken.

Blood collection, safety handling and measurement of related parameters

With the help of a qualified nurse, a wet swab (cotton wool soaked in methylated spirit) was used to clean the cubital fossa. A tourniquet was tied round the arm close to the base of the cubital fossa. A prominent vein was located and with the aid of a 5 ml syringe and needle, 5mls of blood was collected into sample bottles. 1.5 mls of the sample was collected into EDTA sample bottle while 3.5mls was collected into plain sample bottle. After collection of blood sample, the tourniquet was untied and the syringe pulled out. A pressure was immediately applied on the punctured site using a dry swab to achieve haemostasis. Used needles and syringes were disposed into safety box for incineration after blood collection. Blood in the EDTA sample bottle was used for analysis of haemoglobin concentration and glycaeted haemoglobin while serum was obtained from the blood collected into plain sample bottle for analysis of other related parameters.

Measurement of fasting blood glucose

Measurement of fasting blood glucose was done using a glucometer and appropriate strips early in the morning before meal. Each subject was asked to sit and afterwards the procedure was explained to her. After washing of hands and putting on the gloves, a wet swab (cotton wool soaked in methylated spirit) was used to clean the palmar surface of the thumb and allowed to dry. Appropriate test strip was inserted into the glucometer and with a single-use lancet, the thumb was pricked and a drop of blood was applied on the test pad of the test strip and the fasting blood glucose read. Soon after applying the blood drop, a dry swab was applied on the punctured site to obtain haemostasis. The used lancet and test strip were disposed into safety box for incineration.

Measurement of glycaeted haemoglobin level and haemoglobin concentration

Glycaeted haemoglobin level in blood was measured using TD-4611 HbA1c analyser (TAIDOC Technology cooperation, New Taipei City, Taiwan) called the kiptrack analyser which measures HbA1c within the range of 4–16% using an appropriate HbA1c reagent cartridge. The machine was powered on and allowed to boot. After booting, the machine was calibrated using the calibration card of the cartridge pack. The capillary was

pulled out from the cartridge to aspirate blood (about 0.15 micronmeter of blood). The capillary was inserted back into the capillary holder of the cartridge. The cartridge was then inserted into the machine and then the insert button was clicked and the tap was pulled out and then the lid closed to commence measurement. The measurement took about 6minutes for complete processing and measurement (100%) before the result was displaced on the monitor of the machine and this could be read or printed out. Haemoglobin concentration was measured using automated blood cell analyser (Model PCE 210, Japan).

Measurement of blood beta hydroxybutyric acid and serum bicarbonate ion

Beta hydroxybutyric acid was measured using blood hand-held ketometer called keto mojo analyser and test strips (From Napa, Califonia) which read blood ketone levels between 0–3 mmol/l. Each subject was asked to sit and afterwards, the procedure was explained to the subject. After washing of hands and putting on the gloves, a wet swab (cotton wool soaked in methylated spirit) was used to clean the palmar surface of the thumb and allowed to dry. Appropriate test strip was inserted into the ketometer and with a single-use lancet, the thumb was pricked and a drop of blood was applied on the test strip and BHBA level read. Soon after applying the blood drop, a dry swab was applied on the punctured site to obtain haemostasis. The used lancet and test strip were disposed into safety box for incineration.

Serum bicarbonate ion was measured using the principle of ion-selective electrode with the aid of cobas c111 analyser (Roche Diagnostics, Switzerland) which makes use of the principle that certain membrane materials develop an electrical potential (electromotive force, EMF) for the measurements of ions in solution. The electrode has a selective membrane in contact with both the test solution and an internal filling solution. The internal filling solution contains the test ion at a fixed concentration. Because of the particular nature of the membrane, the test ion will closely associate with the membrane on each side. The membrane EMF is determined by the difference in concentration of the test ion in the test solution and the internal filling solution. The complete measurement system for a particular ion includes the ISE, a reference electrode and electronic circuits to measure and process the EMF to give the test ion concentration.

Measurement of serum surfactant protein A

The level of surfactant protein-A (SP-A) in the serum was estimated by the ELISA immunoassay method as reported [13]. Assay was performed in 96-well micro titer plates. Plates were incubated overnight at 4°C with serum. These were then washed extensively with PBS Tween 20 buffer. Two hundred microlitre of rabbit antibodies against SP-A were added to each well and incubated for two hrs at 37°C. Washing was repeated. Bound primary antibodies were detected by incubating the wells with 200 µl of a second antibody, goat anti rabbit IgG conjugated to horse-radish peroxidase. After two hours of incubation, plates were washed again and reacted with substrate (substrate was prepared by adding 34 mg of o-phenylene diamine and 50 µl H_2O_2 to 100 ml of 0.1 M citrate phosphate buffer, pH 5.0). The reaction was terminated by adding 50 µl sulphuric acid to each well and absorbance was read at 492 nm using an ELISA reader. A standard curve was obtained by plotting the absorbance *versus* log of the SP-A concentration. The results were calculated from the mean of triplicate determinations.

Statistical analysis

Data obtained were analysed using IBM SPSS statistical software version 20 and by t-test and results obtained were expressed as mean±SEM and presented in figures while some results were presented in tables. Pearson's correlation and regression analysis was also done to test hypotheses. $P<0.05$ was considered to be statistically significant.

Results

Mean values of anthropometric parameters of Control and DM subjects

As seen in Table 2, the mean age (years) for control and DM subjects were 47.75±1.58 and 50.60±1.85 respectively. From this result, there was no significant difference in mean age between the groups. The mean body weight for control and DM subjects were 69.30±1.18 and 71.75±2.41 respectively. This result presented no significant difference in mean body weight (kg) between the groups. The mean heights for control and DM subjects were 1.71±0.02 and 1.69±0.01 respectively. This result presented no significant difference in mean height (m) between the groups. The mean chest circumference

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Table 2: Mean values of anthropometric parameters of Control and DM subjects.

Parameters	Mean Age (yrs)	Weight (kg)	Height (m)	Chest circumference (cm)
Control	47.75±1.58	69.30±1.18	1.71±0.02	35.65±0.50
DM	50.60±1.85 NS	71.75±2.41 NS	1.69±0.01 NS	35.35±0.59 NS

Note: Values are expressed as Mean±SEM, n=32, NS – non-significant.

(cm) for control and DM subjects were 35.65±0.50 and 35.35±0.59 respectively. From this result, no significant difference existed between the groups.

Mean values of FVC, FEV_1, FEV_1%, SPO_2, O_2 content, Hb FBG in Control and DM subjects

As seen in Table 3, the mean FVC values in control and DM subjects were 4.05±0.25 and 2.44±0.12 (L) respectively. The mean FEV_1 values in control and DM subjects are 3.82±0.10 and 1.92±0.18 (L) respectively. From these results, there was a significant decrease in ($P<0.05$) in FVC and FEV_1 value of DM subjects when compared to control. The mean FEV_1% values in control and DM subjects were 84.40±1.11 and 78.50±3.57 (%) respectively. From this result, there was a significant decrease ($P<0.05$) in FEV_1% value of DM subjects when compared to control but the FEV_1% value of DM subjects was not significantly lower than 80%.

The mean SPO_2 in control and DM subjects were 95.25±0.31 and 81.10±1.03 (%) respectively. The mean haemoglobin concentration in control and DM subjects were 14.24±0.33 and 12.51±0.48 (g/dl) respectively. The mean oxygen content of blood in control and DM subjects were 18.45±0.40 and 14.73±0.61 (vol %) respectively. These results presented a significant decrease ($P<0.05$) in mean SPO_2, Hb concentration, and oxygen content of blood of DM subjects when compared to control.

The mean fasting blood glucose in control and DM subjects were 6.35±0.18 and 11.91±1.07 (mmol/L) respectively. This result presented a significant increase ($P<0.05$) in fasting blood glucose of DM subjects when compared to control.

Mean glycated haemoglobin (HbA1c) in Control and DM subjects

The mean HbA1c in control and DM subjects were 5.58±0.20 and 9.76±0.51 (%) respectively. This result presented a significant increase ($P<0.05$) in mean HbA1c concentration of DM subjects when compared to control (Figure 1).

The percentages of well controlled and poorly controlled DM subjects as indicated by their HbA1c concentrations are seen in Table 4. From the result as contained in this table, well controlled diabetic subjects (that is, subjects with HbA1c concentration below 6.8%) were 15.625% while poorly controlled diabetic subjects (that is, subjects with HbA1c concentration above 6.8%) were 84.375%.

Mean serum surfactant protein-A concentration in Control and DM subjects

The Mean serum surfactant protein-A concentration in control and DM subjects were 3.42±0.18 and 12.36±1.23 (µg/ml) respectively. This result presented a significant increase ($P<0.05$) in mean serum surfactant protein-A concentration of DM subjects when compared to control (Figure 2).

Discussion

From the results for anthropometric parameters, there was no significant difference between the mean age, body weight, height and chest circumference of control when compared to DM subjects. The values of

Table 3: Mean values of FVC, FEV_1, FEV_1%, SPO_2, O_2 content, Hb FBG in Control and DM subjects.

Indices	FVC (L)	FEV_1 (L)	FEV_1% (%)	SPO_2 (%)	O_2 content (Vol %)	Hb (g/dl)	FBG (mmol/L)
Control	4.05±0.25	3.82±0.10	84.40±1.11	95.25±0.31	18.45±0.40	14.24±0.33	6.35±0.18
DM	2.44±0.12*	1.92±0.18*	78.50±3.57*	81.10±1.03*	14.73±0.61*	12.51±0.48*	11.91±1.07*

Note: Values are expressed as Mean±SEM, n=32, * – significantly different from control.

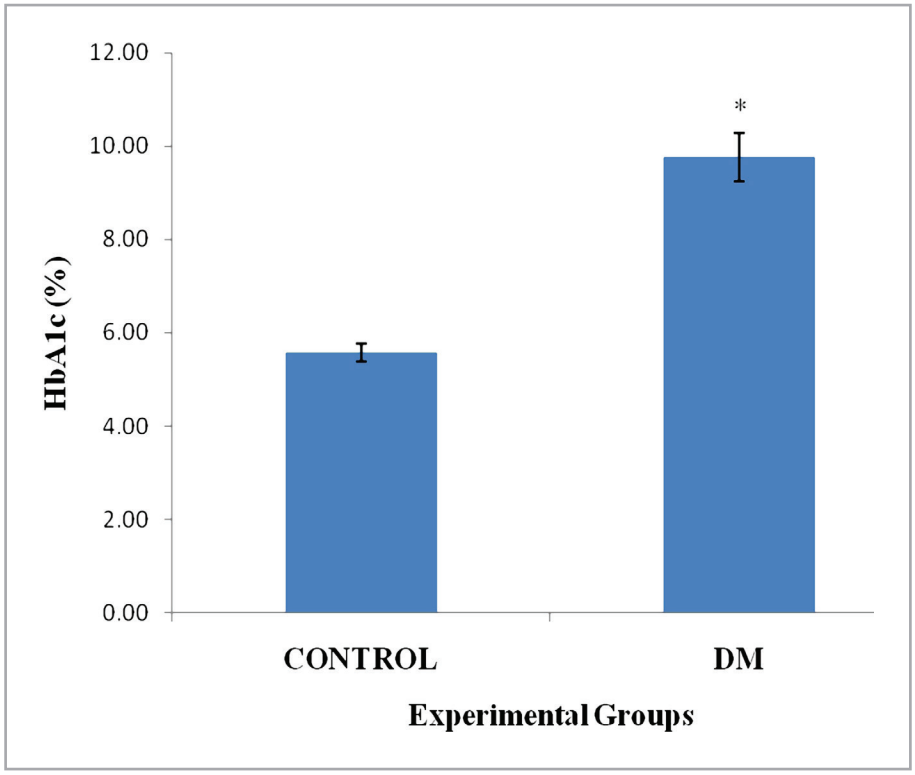

Figure 1: Mean glycated haemoglobin conc. in control and DM subjects. Values are expressed as mean±SEM, n=32, P<0.05, * – Vs control.

anthropometric parameters have been reported to affect lung function indices [14]. Therefore, the anthropometric parameters of control and DM subjects were similar to ensure that any variation in lung function parameters is not as a result of variations in anthropometric parameters.

FVC, FEV_1 and FEV_1% were significantly decreased in DM subjects when compared to control subjects. However, in DM subjects, the mean value of FEV_1 compared to FVC did not show a significant gap, hence the value of FEV_1% seen as (78.50±3.57%). This 78.50±3.57% value of FEV_1% (which is not significantly different from 80%) despite a reduction in FVC and FEV_1 suggest a possible restrictive lung disease. In restrictive lung disease, although FVC and FEV_1 decrease due to restriction in lung expansion and total lung volume, but FEV_1% is normal because there is no significant variation in the value of FVC and FEV_1 because the problem is not obstructive which affects expiration more. Therefore, the decrease in FVC and FEV_1 is due to the decrease in total lung volume but this decrease is in close proportion, hence, the FEV_1/FVC ratio still gives a value of about 0.8 or 80%. The result of this study is in line with the work of Klein [15] and shah [16] who reported a decrease in FVC and FEV_1 of DM subjects, although they reported a decrease in FEV_1% which is in contrast with the result of this study.

HbA1c was significantly raised in DM subjects when compared to control subjects. Diagnosis, management and regular monitoring of the DM are great challenges to both patients and physicians. Glycated haemoglobin provides an accurate and objective measure to access

Table 4: Percentage of well controlled and poorly-controlled DM subjects.

	DM Subjects	
	n	**%**
HbA1c<6.8 (well controlled)	5	15.625
HbA1c>6.8 (poorly controlled)	27	84.375
Total	32	100

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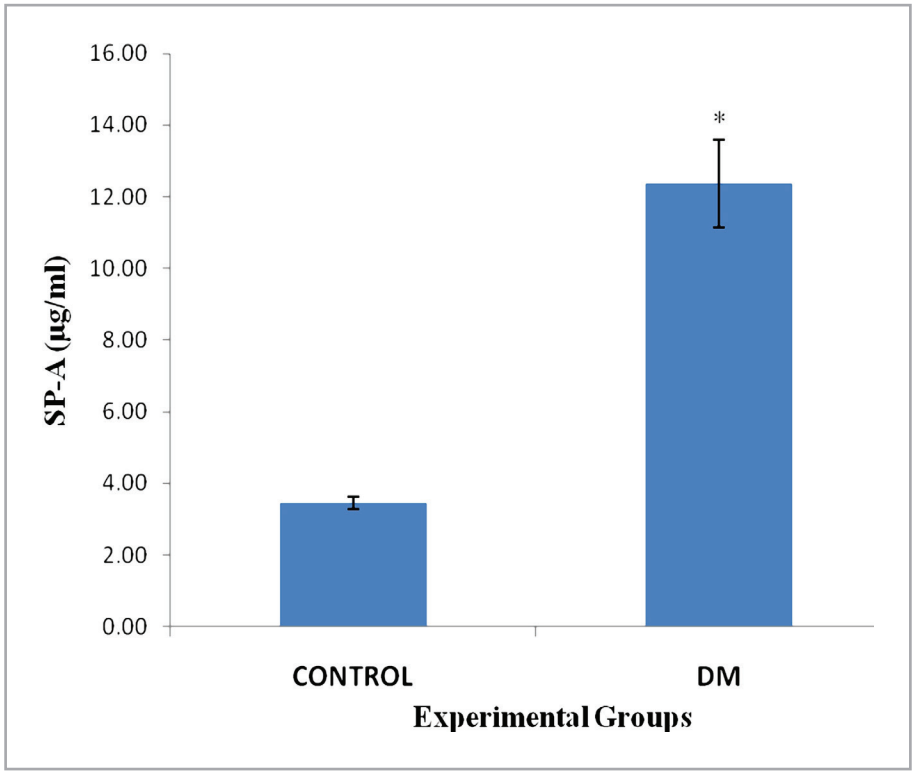

Figure 2: Mean serum surfactant protein A conc. in control and DM subjects. Values are expressed as mean±SEM, n=32, P<0.05, * – Vs control.

the glycaemic control and also to diagnose new cases of DM [17]. In individuals with poorly controlled DM, the quantities of these HbA1c are much higher than in healthy people [18]. The HbA1c level is directly proportional to average blood glucose concentration over the previous 4 weeks to 3 months and provides adequate information for glycaemic control over this period of time. HbA1c of ≤6.5% is considered normal and above this shows poor diabetic control. From the results most diabetic subjects recruited in this study (84.375%) had HbA1c values above 6.5% to as high as above 10.0%. This implies that most my diabetic subjects were poorly controlled or poorly managed.

SP-A was significantly increased in DM subjects when compared to control subjects. Behera [19] asserts that monitoring the level of SP-A in blood may offer new possibilities in the assessment of lung injury. In individuals with normal lungs, SP-A occur in blood in physiological amounts, but in diseases characterized by pulmonary inflammation and pulmonary epithelial injury, there is increased leakage of SP-A into the blood and this can be used to assess the extent of pulmonary parenchymal inflammation. It is established in literatures that there is a critical link between metabolic disorders and inflammation, which leads to a concept called “metaflammation”. Metaflammation is a form of low-grade systemic and chronic inflammation related to excess nutrients and energy [20]. There has been increasing evidence showing inflammatory responses in DM [21]. Chronic low-grade inflammation in DM has given an impetus to the field of immuno-metabolism linking inflammation to insulin resistance and deficiency and many factors advocate a causal link between metabolic stress and inflammation. The value of SP-A, a lung specific inflammatory marker seen in this study is a strong indication of inflammation of the lung parenchymal tissues in DM subjects. Inflammation is a key factor in the etiology of restrictive lung disease. The increase in SP-A level in DM subject in this study suggest that poorly-controlled DM subjects are at risk of restrictive lung disease associated with inflammation.

Hyperglycemia is regarded as the major upstream mechanism while micro-inflammation is regarded as the subsequent downstream driving force of diabetes related complications [22]. Numerous cellular factors trigger inflammatory signaling cascades in DM and as a result DM is at the moment considered an inflammatory disorder triggered by disordered metabolism [23]. Several inflammatory cytokines save as markers for tissue inflammation, hence injury. A lung specific inflammatory cytokine called surfactant protein A is an important index in assessing the inflammation of the alveoli of

various etiologies and has been reported to increase in smokers [19]. From the result of this study, the increase in SP-A is a strong indication of alveolar inflammation in diabetic subjects, especially the poorly controlled.

Percentage oxygen saturation, Hb level and oxygen content were all significantly reduced in Dm subjects when compared to control subjects. Percentage oxygen saturation of blood depends on some factors such as the surface area of the respiratory membrane which the alveoli contribute immensely. Therefore, the significant increase in SP-A as seen in this study which is a strong indication of alveolar inflammation suggest a lost in number of functional alveolar and consequent reduction of the surface area needed for oxygen saturation.

The reason for the reduction in Hb level of DM subjects seen in this study is not so clear, although it may be attributed to the increase in HbA1c seen in this study and consequently, a reduction in the level of normal haemoglobin. In this study, oxygen content of blood was also reduced in diabetic subjects. Several factors such as haemoglobin levels, oxygen saturation and perfusion are notable factors that affect oxygen content of blood. The reduction in oxygen content of blood of DM subjects as seen in this study may be a consequence of reduced haemoglobin level as well as reduced percentage oxygen saturation as shown in this study.

Conclusion

The results of this study incite a call for concern on the pulmonary function of diabetes mellitus patients. The results of this study strong indicate that poorly controlled DM patients are at risk of restrictive lung disease as seen in reduced FVC, FEV_1 but normal FEV_1% as well as changes in related parameters (SP-A, HBA1c, SPO_2 and O_2 content of blood) which could offer some pathophysiological explanation. There is therefore the need for regular monitoring of lung function status of diabetic patients, especially the poorly controlled.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Ethical approval was sought and obtained from the Health Research Ethics Committee (HREC) of the University of Calabar Teaching Hospital (UCTH) before commencement of the research. The HREC Protocal Assigned Number was UCTH/HREC/33/633.

Consent to participate

Written informed consent was obtained from all the participants.

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