Pulmonary tuberculosis and diabetes mellitus co-morbidity in a Nigerian tertiary hospital

FC Ugoeze, PU Ele, AE Anyabolu, EH Enemuo, RC Okonkwo, EO Umeh, IU Ezeani, UU Onyeonoro

Abstract

Background: Pulmonary tuberculosis (PTB) and Diabetes Mellitus (DM) co-morbidity is an increasing problem in Nigeria. Patients may present with atypical clinical findings compared with PTB-only patients, posing a diagnostic challenge.

Objective: To determine the prevalence of PTB-DM co-morbidity at Nnamdi Azikiwe University Teaching Hospital NAUTH Nnewi, and identify the clinico-radiographic differences between the co-morbid group and the PTB-only group.

Methods: 120 newly diagnosed, consenting PTB patients were recruited for the study. Demographic and clinical data were obtained using a simplified questionnaire. PTB diagnosis was defined as positive sputum smear microscopy for acid fast bacilli in at least 2 sputum specimens in patients with suggestive symptoms of PTB. DM was diagnosed using random blood glucose of greater than or equal to 11.1mmol and fasting blood glucose greater than or equal to 7.0mmol/l. Chest radiographs were performed for the patients and assessed for features that are suggestive of pulmonary tuberculosis. The outcome was analysed using appropriate statistics. The primary outcome for the study is the prevalence of the co-morbidity among the newly diagnosed PTB patients.

Results: Co-morbidity of PTB-DM was confirmed in 22/120 (18.3%) of the recruited patients. New DM diagnosis was made in 5/22 (22.7%) of the population. Co-morbid patients were found to be significantly older and likely to be more hypertensive ($\chi 2$ =15.94, p<0.001) than the PTB-only group. Whilst cough and weight loss were the most common symptoms, we found that anorexia was significantly higher in the co-morbid group ($\chi 2$=3.85, p = 0.016). We found no difference in radiographic characteristics between the two groups.

Conclusion: The prevalence of PTB-DM co-morbidity in this study was high and confirmed an increasing trend when compared with previous literature. PTB presentation represents an opportunity to screen and initiate treatment for non-communicable diseases such as diabetes mellitus.

FC Ugoeze, PU Ele, AE Anyabolu and EH Enemuo: Respiratory Unit, Department of Internal Medicine, Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Nigeria. RC Okonkwo: Microbiology section, Directly Observed Treatment Short course (DOTS) Unit, NAUTH Nnewi. EO Umeh: Department of Radiology, NAUTH Nnewi. IU Ezeani: Endocrinology and Metabolism Unit, Department of Internal Medicine, Federal Medical Centre, Umuahia, Nigeria. UU Onyeonoro: Department of Community Medicine, Federal Medical Centre, Umuahia. Correspondence: ociso@yahoo.com.

Pulmonary tuberculosis (PTB) is a bacterial infection of the lungs caused by Mycobacterium tuberculosis complex. It remains a source of global concern. An estimated 10 million people developed tuberculosis (TB) in 2018 and about 1.45 million died from the disease, making TB the leading cause of death from a single infectious agent worldwide.[1]

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglyceamia.[2] Globally, an estimated 425 million people live with DM (20-79 years), a number which is expected to grow to at least 629 million by the year 2045.[3]

Diabetes mellitus increases the risk for development of PTB threefold compared to healthy population.[4, 5, 6] With this global increase in the cases of DM, a new threat is therefore posed to the current incidence of PTB. A resurgence of PTB in endemic regions is therefore likely with a potential risk of global spread with serious implication for TB control.

In 2001, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) launched the bidirectional screening for TB and DM. They recommended among other things the screening of TB among DM patients in countries with TB prevalence above 100/100,000 population as well as screening of DM among TB patients in all countries.[7] Some countries including Nigeria are yet to incorporate this into their national TB programme.

Variable figures of the prevalence of PTB-DM co-morbidity ranging from 5.7-30% have been reported globally.[6,8-11] Past studies on the prevalence of PTB-DM co-morbidity in Nigeria have shown an increasing trend over the years.[8,9] A literature search showed paucity of data on the prevalence of PTB-DM in the south-eastern Nigeria. This study therefore aims to fill this research gap, as well as generate evidence for designing programmes for co-management of TB-DM in the country.

Methodology

This is a cross sectional study of patients presenting at various departments at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, with symptoms suggestive of PTB. All consenting adults of 18 years of age and above seen at DOTS clinic, Medical Outpatients (MOP), Accident and Emergency (A&E) department, General Outpatients (GOP) department and medical wards, with features suggestive of PTB and confirmed to have active TB disease were recruited. Patients who were newly diagnosed with PTB (anti-TB drug naive) were consecutively enrolled into the study from September 2013 to July 2014. Patients who were diagnosed with Human Immunodeficiency Virus (HIV) infection, patients who were

Table 1: Patients' demographics, Presenting Symptoms and Comparisons of Characteristics between PTB-only and PTB-DM subgroups

	PTB only n=98 (%)	PTB-DM n=22 (%)	Total N=120 (%) {M/F}	t-test	P-value
Age (in years)					
≤30	39 (39.8)	1 (4.5)	40 (33.2){22/18}		
31-40	24 (24.5)	5 (22.5)	29 (24.2){19/10}		
41-50	17 (17.3)	6 (23.7)	23 (19.2){14/9}		
51-60	10 (10.2)	7 (31.8)	17 (14.2){12/5}		
>60	8 (8.2)	3 (13.6)	11 (9.2){9/2}		
Mean±SD	37.5+14.4	48.9+11.2	39.5±14.5	3.49	0.001*
Gender				**X^2**	**p-value**
Males	62(63.3)	14(63.6)	76(63.3)		
Females	36(36.7)	8(36.4)	44(36.7)	0.001	0.97
Symptoms				**X^2**	**p-value**
Cough	98(100)	22(100)	120(100)	-	-
Weight loss	95(96.9)	22(100)	117(97.5)	-	-
Fatigue	84(85.7)	19(86.4)	103(85.7)	0.006	0.94
Fever	81(82.7)	15(68.2)	96(80.0)	2.35	0.13
Night sweat	71(72.4)	19(86.4)	90(75.0)	1.86	0.17
Dyspnea	73(74.5)	9(40.9)	82(68.3)	2.10	0.15
Chest pain	70(71.4)	14(63.6)	84(70.0)	0.52	0.47
Haemoptysis	37(37.8)	11(50.0)	48(40.0)	1.12	0.29
Anorexia	59(60.2)	15(68,2)	74(61.7)	3.85	0.016*
Polyuria	18(18.4)	16(72.7)	34(28.3)	26.15	0.000*
Visual impairment	21(21.4)	11(50.0)	32(26.7)	7.50	0.006*
Polydipsia	16(16.3)	13(59.1)	29(24.2)	17.92	0.006*
Foot ulcer	2(2.0)	1(4.5)	3(2.5)	0.46	0.50
Blood pressure				**X^2**	**p-value**
Normal BP	92(93.9)	14(63.4)	106(88.3)		
Hypertension	6(6.1)	8(36.4)	14(11.7)	15.94	0.000*

*n=120 *Significant; M-males; F-females; BP-blood pressure*

unconscious, pregnant women and those with prior history of PTB were excluded from the study.

Ethical clearance was obtained from the Ethics Committee of Nnamdi Azikiwe University Teaching Hospital Nnewi. Those that participated in this study did it voluntarily, and they signed an informed consent before enrolment after due clarification of the rationale, goals, benefits, and risks of the study.

A simplified questionnaire was used to collect patient demographics and clinical data for consenting participants. Questions were asked by the researcher in English and/or local language where necessary.

In line with the prevailing National guideline which was operational in the hospital during the time of study,[12] three sputum specimens (spot, morning, and spot) were collected from each patient which were subjected to Ziehl-Neelsen staining and smear microscopy at the NAUTH TB laboratory. It is however noteworthy that current guideline recommends the use of at least 2 sputum samples for smear microscopy or a single sputum specimen for Xpert MTB/RIF testing in a quality assured laboratory.[13] Diagnosis of PTB in this study was based on the presence of acid fast bacilli in at least 2 sputum specimens of patient who presented with PTB symptoms.[14]

The random and fasting venous blood specimens of the recruited patients were collected for DM screening and confirmation respectively. Diagnosis of DM was based on WHO criteria of random blood glucose of greater than or equal to 11.1mmol and fasting blood glucose greater than or equal to 7.0mmol/l.2. Two significant results in asymptomatic patients or one in a symptomatic patient was required. A chest radiograph was done for each patient which was interpreted by two radiologists – each film double read to ensure quality control. The chest radiographs were assessed independently by the radiologists for features that are suggestive of pulmonary tuberculosis, such as the following features in various combinations: cavity, coin lesions, pleural effusion, apical pleural thickening and pneumonic consolidation.[15]

Table 2: Occupation of the study participants

Occupation	Frequency (%)	
Traders	50	(41.7)
Students	19	(15.8)
Artisans	11	(9.2)
Transport workers	8	(6.7)
Farmers	6	(5.0)
Housewives	6	(5.0)
Apprentices	5	(4.2)
Civil servants	4	(3.3)
Employees (private company)	3	(2.5)
Teachers	2	(1.7)
Unemployed	2	(1.7)
Retirees	2	(1.7)
Health workers	1	(0.8)
Clergy	1	(0.8)

n=120

The data was analysed using Statistical Package for Social Science (SPSS) version 20 (2012) IBM Corp Armonk, NY, USA. Frequencies and proportions of the categorical variables as well as the means and standard deviations of the continuous variables were obtained. Chi-squared test was used to test the association between gender and PTB-DM co-morbidity, while Student's t-test was used to test the association between age and PTB-DM co-morbidity. The P value of less than 0.05 was regarded as significant.

Results

A total of 120 newly diagnosed PTB patients were recruited over the period of study. Twenty two out of the 120 newly diagnosed patients were found to be diabetic giving a prevalence of 18.3%. Seventeen out of the 22 patients (77.3%) with DM were known diabetic patients of varying duration from time of diagnosis (1-12 years), while 5/22 (22%) were newly diagnosed with DM during the period of study and subsequently commenced on anti-diabetic treatment. The age range of the recruited participants was from 18 years to 79 years (range of 61 years). The mean age of all participants was 39.5 ± 14.5 years. Though the mean age of male patients was higher than the female (41.2±14.8 vs 36.7±13.5), the male participants were not significantly older than the females (p = 0.11).

Majority (57.4%) of the newly diagnosed PTB patients were young people, with greater proportion being less than 30 years of age (Table 1). There were 76 (63.3%) male and 44 (36.7%) female participants giving a male-to-female ratio of 1.7:1. The male to female ratio was found to be similar in both PTB-only and co-morbid subgroups (Table 1).

The mean age of the PTB-DM co-morbid patients was 48.9 ± 11.2 years while that of the PTB only subgroup was 37.5 ± 14.4 years. Table 1 below shows that the co-morbid patients were significantly older than the PTB only patients (t =3.49, p=0.001).

Pulmonary tuberculosis was found to be commonest among traders (41.7%) in this study (Table 2), followed by students (15.8%), artisans (9.2%) and transport workers (6.7%). Health workers (0.8%) and clergy (0.8%) were the least affected.

Cough was found to be universal and along with weight loss, was the most common symptom. Anorexia was significantly higher in the co-morbid patients than PTB only patients ($\chi 2$=3.85, p = 0.016). The co-morbid patients had higher proportion for weight loss (100%), night sweats (86.4%), fatigue (86.4%) and haemoptysis (50%) though not statistically significant. The DM specific symptoms – polyuria, polydipsia and visual impairment – were, significantly higher in the co-morbid patients (Table 1).

The mean systolic and diastolic pressures in the 120 participants studied, were 109.4 ± 15.4 mmHg and 70.6 ± 10.9 mmHg respectively. Co-morbid patients were more likely to have higher mean systolic (t=3.59, p<0.001) and diastolic blood pressures (t=2.80, p=0.006) than PTB only subgroup. The diagnosis of hypertension was significantly higher in the co-morbid patients ($\chi 2$ =15.94, p<0.001) (Table 1).

One hundred and fifteen chest radiographs of reportable quality were retrieved and features in all were in keeping with pulmonary tuberculosis. Pneumonic consolidation and cavitary lesions were the most common radiographic features found in 110/115 (95.7%) and 105/115 (91.3%) of the patients respectively. Coexisting pleural effusion was not a common feature present in this cohort.

Discussion

There is a renewed interest in synergistic relationship between PTB and DM both in Nigeria and globally. Published literatures demonstrate a gradual increase in the prevalence of PTB-DM co-morbidity in Nigeria over time. Adeyeye et al[8] in their study reported a prevalence of 5.7% in 2013 while Ogbera et al[9] reported a prevalence of 12.3% in 2014, having recruited 4000 TB patients from 56 DOTS centres in Lagos. We found that the prevalence of DM among the newly diagnosed PTB participants in this study was 22/120 (18.3%) which represented a figure higher than those earlier published. This is important because of the possible impact of DM on PTB outcome.

This increase could partly be explained by the increasing prevalence of DM in the general population,[3] leading to a pro rata increase in the DM population among PTB patients. Also, DM being an independent risk factor for the development of PTB would invariably raise the proportion of co-morbidity. The figure, however, is comparable with the prevalence of PTB-DM co-morbidity reported in international studies ranging from 15% to 30%.[6,10,11,16]

This study also demonstrated the importance of screening all PTB patients for diabetes mellitus. Five out of 22 (22.7%) DM patients were diagnosed during this study and commenced on appropriate therapy. A study reported new DM diagnosis in 64% of the PTB-DM co-morbid patients.[9] These findings obviously lend credence to the importance of screening DM among all TB patients in all countries as recommended by WHO and IUATLD. Routine screening of all PTB patients could also serve as a gateway in the diagnosis of the large populations of DM patients who remain undiagnosed (50% of adults with diabetes).[3]

The co-morbid subjects in this study were significantly older than the PTB only group. This agrees with the findings of some

studies that PTB-DM co-morbidity is associated with older age.[11,17,18,19] The explanation for this could be that DM(especially type 2) is associated with increasing age.[20] This finding becomes significant when considering PTB outcome. Two factors – co-morbidity and older age of patients – stand out for consideration when discussing PTB outcome. Generally, poorer outcome of diseases, including deaths are associated with increasing age.[21,22,23] Furthermore, Wang et al[24] found that PTB-DM patients showed higher frequencies of fever, haemoptysis, positive AFB sputum smears and consolidation, cavity and lower lung field lesion on chest radiographs, and higher mortality rate compared to patients with PTB only. These two important characteristics of PTB-DM co-morbidity invariably paint a bleak outcome for co-morbid patients, making routine DM screening imperative.

Similar to the findings of this study, Baghaei et al[25] reported cough and weight loss as the commonest symptoms among the 149 PTB patients studied in Iran. Universality of cough among the studied patients depicted the involvement of pulmonary parenchyma in pathogenesis of PTB with alveolar space infiltration (consolidation) and cavitary lesions. Jabbar et al[26] however reported fever as the commonest symptom, followed by cough among the 173 PTB patients with diabetes mellitus in Pakistan.

Anorexia was the only symptom found to be significantly higher in the co-morbid group than the PTB-only group. Anorexia is a consequence of the systemic effect of the cytokines elaborated by the activated macrophages and T- lymphocytes (TNFα, IFNγ).[27] Significant occurrence of anorexia in the co-morbid group could partly be attributed to higher levels of innate and type 1 cytokines resulting from paradoxical hyper-inflammatory response seen in PTB-DM patients with chronic hyperglycemia but not in PTB-only patients.[28,29,30] Moreso, PTB-DM patients are shown in this study to be older. Studies have shown that anorexia is highly prevalent among older adults.[31,32,33]

The blood pressure values of the majority of the newly diagnosed PTB patients (88.3%) were within normal range with the mean systolic and diastolic blood pressure of 109.4±15.4 mmHg and 70.6±10.9 mmHg respectively. The co-morbid participants, however, were significantly more hypertensive than the PTB only group ($\chi 2=15.94$, $p<0.001$). This could partly be due to the known association of DM with hypertension. Isezuo et al[34] demonstrated this in their study by showing that 54.3% of the 254 type 2 DM patients had concurrent DM and hypertension. Similarly, studies have shown that the prevalence of hypertension increases with age.[35,36] The older age of the PTB-DM co-morbid patients as shown by this study could therefore explain this trend.

Pneumonic consolidation and cavitary lesions were the commonest Chest X-ray findings in this study. Comparison between the diabetic and non-diabetic patients did not show significant difference in these features. Siddiqui AM[37] reported that tuberculosis has similar radiologic presentations in both diabetics and non-diabetics. Other studies[38,39] however reported that chest radiographic findings in diabetics with PTB depart from the typical presentations.

Limitations of this study are the smaller sample size used which may affect the power of the comparison between the two subgroups. The study also could not establish actual causal relationship beyond association.

Conclusion

This study has found that the prevalence of PTB-DM co-morbidity was 18.3% which represented an increasing trend. Differences exist between the PTB only and the co-morbid groups and this becomes important in management of these patients. The usefulness of screening all PTB patients for DM was obvious, one of which is identifying new DM patients. Policy makers should include DM screening in the guideline for PTB management in Nigeria. Also PTB- DM collaborative activities should be established in Nigeria involving experts in the relevant areas.

We recommend further studies using larger sample size with the view to establishing causal relationships.

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Author declaration

Competing interests? None. Any ethical issues involving humans or animals? None. Was Informed Consent required from any patient or next of kin involved in the study? At the point of recruitment, the study participants were duly informed about the purpose of the research. The expectations of the researchers from the participants were properly communicated to them, including providing their personal information through questionnaire, blood sample for blood glucose estimation, chest radiography, all of which were paid for by the researchers. The participants were told about their choice to participate or to opt out at any stage of the research without any consequences to them. They were also assured of their confidentiality during and after the study. A consent form was given to each participant to sign after understanding the above information and agreeing to be part of the study. A copy of the signed ethical approval for the study from the University Ethics Committee has been submitted to AJRM

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