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Prognostic factors among TB and TB/DM comorbidity among patients on short course regimen within Nairobi and Kiambu counties in Kenya

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ABSTRACT

Background: The double burden of diabetes mellitus (DM) and pulmonary tuberculosis (TB) is one of the global health challenges. Studies done in different parts of the world indicate that 12%-44% of TB disease is associated with DM. In Kenya TB-DM co-morbidity data is scarce and is not readily available. In this study we set to determine the difference in treatment outcomes among TB and TB/DM comorbidity patients and their respective clinical and socio-demographic characteristics.

Objective: To determine prognostic factors among TB and TB/DM comorbidity among patients on short course regimen within Nairobi and Kiambu counties in Kenya.

Methods: We carried out a prospective cohort study of non-pregnant patients aged 15 years and above that tested positive for TB in two peri-urban counties in Kenya between February 2014 and August 2015. Clinical and socio demographic data were obtained from a questionnaire and medical records of the National TB program patient data base at two, three, five and six months. The data consisted of TB status, HIV status, TB lineage, County, (Glucose, %HbA1c, creatinine) weight, height, BMI, regimen, sex, level of education, employment status, distance from health facility, number of cigarettes smoked, home size, and diet. Univariate analysis was then used to compare each potential risk factor in the TB and TB/DM patients by the Pearson x^2 test of proportions or fisher exact test, as appropriate.

Results: DM prevalence (HbA1c > 6%) among TB infected patients was 37.2%. Regimen, employment status, alcohol intake, smoking, age and household size were some of the factors associated with DM among TB patients at p-value < 0.05. The number of cigarettes smoked per day and the value of the BUN were significant risk factors of developing DM among TB patients (p values = 0.045). Mean time to conversion from positive to negative was slightly higher for the TB-DM patients compared to the TB patents, though not statistically significant (p = 0.365).

Conclusion: Patients regimen, employment status, alcohol intake, smoking, age and are associated with DM among TB patients.

Introduction

Infectious and chronic disease co-morbidity is often due to mutual risk factors as well as direct interaction [1–3]. Currently one of the global health challenges is the double burden of diabetes mellitus (DM) and pulmonary TB [4,5]. In 2015WHO global reports indicated an annual new tuberculosis (TB) case detection of 10.4 million out of which 1.8million resulted in death (WHO, 2016), while DM had 415 million cases out of which 5 million resulted in fatalities [6–8]. TB and DM co-morbidity is well documented in low and medium income countries (LMIC) accounting for 95% and 75% of TB, and DMcases respectively [2,4]. This rising DM epidemic in LMIC already burdened with TB, may threaten some of the gains made by TB control programs [5].

Studies done in different parts of the world indicate that 12–44% of TB disease is associated with DM [4,9]. DM triples the risk of developing active TB among infected individuals [10–12] by directly impairing the innate and adaptive immune responses that are necessary to counter the progression of the infection [10,11]. Association between TB and DM is supported by the fact that DM is a known to impair mediated immunity that increases susceptibility to develop TB disease and increase the risk of relapse. In addition active DM adversely affects TB treatment outcomes by delaying microbiological response [13,14].

Despite the collaborative framework for care and control by WHO guidelines on TB-DM co-morbidity management (WHO 2011), most

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sub-Sahara African countries still lag behind in screening all TB patients seeking care for DM [15,16]. With a point prevalence of 558 per 100,000 according to the National Tuberculosis, Leprosy and Lung Program (NLTD) prevalence survey of 2017, Kenya is one of the top 22 countries in the world in regards to high TB disease burden. Though unpublished reports indicate higher rates of non-communicable resultant deaths, reported data indicates it contributed to 1% of notified fatalities [17–19]. This indicates a dearth of data or underestimation of the disease burden and consequently TB-DM co-morbidity worldwide. In Kenya, TB-DM co-morbidity data is scarce and is not readily available. In this study we set to estimate the prevalence of DM among newly diagnosed TB cases and associated risk factors at randomly selected health facilities in Nairobi and Kiambu counties in Kenya. We evaluated the difference in treatment outcomes among TB and TB-DM co-morbidity patients in line with the Kenya National TB Program treatment guidelines recommending that all patients with TB use standardized short regimens for treatment.

Material and methods

Study design

We carried out a prospective cohort study in two counties, Kiambu and Nairobi, in Kenya between February 2014 and August 2015. Patients aged above15 years who tested positive for Mycobacterium tuberculosis complex on sputum smear microscopy and were not pregnant at the time of diagnosis were eligible to participate. Ethical approval for the study was obtained from the Kenyatta National Hospital Ethical Research Committee (KNH/UoN-ERC) and the study was undertaken in accordance with the principles of the Helsinki Declaration.

Written consent was obtained from patients who agreed to participate. Venous blood drawn was collected at baseline in two separate tubes (one for fasting or random blood glucose levels and the other for HbA1c levels). This was followed by physical examination and questionnaire administration by trained healthcare personnel where detailed history, including signs and symptoms of diabetes mellitus, cigarette smoking and other life-style information were ascertained. Patients were then followed at two, three, five and six months and at end of therapy to assess adherence and clinical evaluation with sputum microscopy examination at each time when possible. The initial sputum examination was submitted for culture and pathogen identification. Patients were examined at each visit for both TB and DM.

Care and treatment

Newly diagnosed tuberculosis patients were put on a six-month category I regimen comprising of 2 months of isoniazid, rifampin, pyrazinamide and ethambutol followed by four months of isoniazid and rifampin. Previously treated patients, including those who had failed prior therapy were put on category II regimen which is similar to category I except, streptomycin is included in first two months, while pyrazinamide is prolonged by one month and isoniazid, rifampin and ethambutol are given for an additional five months. Dosing was as per daily fixed dose combinations formulations as per NTLD and WHO guidelines, which were given using Directly Observed Treatment, Short-Course (DOTs) [20].

Data analysis

Clinical and social demographic data were obtained from the administered questionnaire and medical records of the National TB program patient data base. The data consisted of TB status, HIV status, TB lineage, County, (Glu, %HbA1c, Creatinine) weight, height, BMI, regimen, sex level of education, employment status, distance from facility, number of cigarettes smoked, home size, and diet. Univariate

Table 1
Socio-demographic characteristics of the patients with TB and TB-DM co-morbidity.

	TB (n = 347) n (%)	TB-diabetic (n = 129) n (%)	TB-not diabetic (n = 218) n (%)
Age categories			
Median age (IQR)	31 (13)	32 (13)	31 (13)
Under 30	163 (47)	59 (45.74)	104 (47.71)
31–40	130 (37.5)	54 (41.9)	76 (34.9)
41–50	40 (11.5)	9 (7)	31 (14.2)
51–60	11 (3.2)	6 (4.7)	5 (2.3)
Over 60	3 (0.9)	1 (0.8)	2 (0.9)
Gender			
Female	98 (28.2)	36 (27.9)	62 (28.4)
Male	249 (71.8)	93 (72.1)	156 (71.6)
Education level			
No school	15 (4.3)	5 (3.9)	10 (4.6)
Primary	116 (33.4)	37 (28.7)	79 (36.2)
High school	158 (45.5)	61 (47.3)	97 (44.5)
College	58 (16.7)	26 (20.2)	32 (14.7)
Employed			
Yes	233 (67.1)	79 (61.2)	154 (70.6)
No	114 (32.9)	50 (38.8)	64 (29.4)
Income			
<1000	87 (25.1)	29 (22.5)	58 (26.9)
1001–5000	66 (19)	29 (22.5)	37 (17.1)
5001–10,000	84 (24.2)	27 (20.9)	57 (26.4)
>10,000	108 (31.1)	44 (34.1)	64 (29.6)
Missing data	2 (0.6)		
Ever drank alcohol			
Missing data	1 (0.3)	0 (0)	1 (0.5)
NA	54 (15.6)	26 (20.2)	28 (12.8)
No	137 (39.5)	53 (41.1)	84 (38.5)
Yes	155 (44.7)	50 (38.8)	105 (48.2)
Ever smoked			
Missing data	1 (0.3)	0 (0)	1 (0.5)
NA	7 (2)	4 (3.1)	3 (1.4)
No	240 (69.2)	90 (69.8)	150 (68.8)
yes	99 (28.5)	35 (27.1)	64 (29.4)
No of cigarettes daily*			
Missing data	67 (67.7)	21 (60)	46 (71.9)
<20	24 (24.2)	9 (25.7)	15 (23.4)
>20	8 (8.1)	5 (14.3)	3 (4.7)
Health seeking frequency			
Missing data	1 (0.3)	0 (0)	1 (0.5)
Once a year	163 (47)	63 (48.8)	100 (45.9)
Other	75 (21.6)	30 (23.3)	45 (20.6)
RARE	1 (0.3)	0 (0)	1 (0)
Twice a_year_more	107 (30.8)	36 (27.9)	71 (32.6)
Distance from the facility			
Missing data	1 (0.3)	0 (0)	1 (0.5)
0–10KM	245 (70.6)	95 (73.6)	150 (68.8)
11–20KM	84 (24.2)	28 (21.7)	56 (25.7)
21–30KM	16 (4.6)	5 (3.9)	11 (5)
>30KM	1 (0.3)	1 (0.8)	0 (0)
Facility			
Missing data	1 (0.3)	0 (0)	1 (0.5)
Government	224 (64.6)	80 (62)	144 (66.1)
Government_ NGO_mission	4 (1.2)	2 (1.6)	2 (0.9)
Government_ other	1 (0.3)	0 (0)	1 (0.5)
Government_ Traditional	2 (0.6)	0 (0)	2 (0.9)
NG0_mission	5 (1.4)	2 (1.6)	3 (1.4)
Private_clinic	60 (17.3)	27 (20.9)	33 (15.1)
Private_clinic Government	49 (14.1)	18 (14)	31 (14.2)
Private_clinic other	1 (0.3)	0 (0)	1 (0.5)
Household members			
<2persons	194 (55.9)	65 (50.4)	129 (59.2)
>2persons	153 (44.1)	64 (49.6)	89 (40.8)
Diet			
Fats	59 (17)	27 (20.9)	32 (14.7)
Sugars, Vegetables	4 (1.2)	0 (0)	4 (1.8)
Vegetables, Meat	3 (0.9)	2 (1.6)	1 (0.5)
Vegetables	1 (0.3)	0 (0)	1 (0.5)
Sugars, Vegetables, Meat	2 (0.6)	0 (0)	2 (0.9)
Fats, Meat	1 (0.3)	0 (0)	1 (0.5)
Fats, Sugars	28 (8.1)	13 (10.1)	15 (6.9)

(*continued on next page*)

analysis was then used to compare each potential risk factor in the TB and TB/DM patients by the Pearson x^2 test of proportions or fisher exact test, as appropriate. To identify the factors that are independently associated with the outcome of TB/DM, we performed multiple logistic regression analysis. We further used forward stepwise approach to add covariates to the model. All factors with biological plausibility and $p < = 0.2$ in the univariate analysis were considered in the multiple regression models. To test for significant interaction terms, we used Hosmer–Lemeshow test to estimate the goodness of fit of the logistic regression model.

Results

347 TB patients were surveyed from 2 counties: Nairobi (290, 83.6%) and Kiambu (57, 16.4%). The age range of the patients was between 15 and 85 years with the median age of 31 (13) years. Majority of the patents surveyed (47%) were less than 30 years with only 0.9% being over 60 years. 98 females and 249 males were enrolled in the study. About 67% of the study population was employed with 31.1% earning more KSH. 10,000. The education levels of the participants were as follows; 4.3% had no education, 33.4% had primary level, 45.5% with high school and 16.7% with collage level education. . Other socio-demographic and clinical characteristics of the patients are shown in Table 1.

Using the diagnostic criteria (HbA1c > 6%), the prevalence of diabetes among TB patients in this study was found to be 37.2%. Out of the 129 with DM, 20.9% were diagnosed with HIV and 1.6% still tested positive at the 6-month smear for TB. The median age of patients with TB and DM was 32 (IQR = 13) years. This was slightly higher than those without TB (31 years, IQR = 13 years). The prevalence was found to be slightly higher in males compared to females; in those on 2RHZE/4RH regimens than on 2SRHZE/1RHZE/5RHE although these differences were not statistically significant. These results are in Tables 1 and 2.

Univariate binary logistic regressions indicated that the number of cigarettes smoked per day and the value of the BUN were significant risk factors of developing DM among TB patients (results in Table 4). Those patients taking < 20 cigarettes a day are less likely to develop DM compared to those that take > 20 cigarettes a day (p values = 0.045). A unit increase in BUN increases the odds of diabetes by 1.211 times. The rest of the variables included from the univariate analysis were not significant risk factors of developing DM. None of the risk factors were found to be significant in the multiple logistics regression.

Of 347 patients with TB enrolled in the study, 303 (87.3%) had recorded smear negative at month 6 TB test with 0.6% still testing positive. Overall, the mean time to conversion among those who switched from smear positive to smear negative was 3.16 (SD = 0.57) months and the median conversion time being 3 (IRQ = 0) months. The mean time to conversion was slightly higher for the TB-DM patients compared to the TB patents. This difference was however not statistically significant (See results in Table 5). The non-statistical significant results were further seen in the median time to conversion, which was

Table 1 (*continued*)

	TB (n = 347) n (%)	TB-diabetic (n = 129) n (%)	TB-not diabetic (n = 218) n (%)
Fats, Sugars, Meat	107 (30.8)	37 (28.7)	70 (32.1)
Fats, Sugars, Vegetables	6 (1.7)	1 (0.8)	5 (2.3)
Fats,Sugars, Vegetables,Meat	32 (9.2)	14 (10.9)	18 (8.3)
Meat	15 (4.3)	6 (4.7)	9 (4.1)
Sugars	74 (21.3)	26 (20.2)	48 (22)
Sugars, Meat	15 (4.3)	3 (2.3)	12 (5.5)

This is a descriptive table indicating the socio-demographic characteristics (Age, gender, education level, Employment, Income, alcohol intake, smoking habit, health seeking behaviors, health care facility, house hold size and the diet) of the patients with TB and TB-DM comorbidity

Table 2
Clinical presentations of the patients with TB and TB-DM comorbidity.

	TB (n = 347) n (%)	Diabetic (n = 129) n (%)	Not diabetic (n = 218) n (%)
HIV status			
ND	25 (7.2)	11 (8.5)	14 (6.4)
Negative	245 (70.6)	91 (70.5)	154 (70.6)
Positive	77 (22.2)	27 (20.9)	50 (22.9)
Regimen			
2RHZE/4RH	315 (90.8)	120 (93)	195 (89.4)
2SRHZE/1RHZE/5RHE	32 (9.2)	9 (7)	23 (10.6)
Smear month 6			
Missing data	1 (0.3)	0 (0)	1 (0.5)
ND	51 (14.7)	23 (17.8)	28 (12.8)
Negative	292 (84.1)	104 (80.6)	188 (86.2)
Positive	3 (0.9)	2 (1.6)	1 (0.5)
Outcome			
C	292 (84.1)	104 (80.6)	188 (86.2)
D	6 (1.7)	3 (2.3)	3 (1.4)
F	3 (0.9)	2 (1.6)	1 (0.5)
NC	4 (1.2)	3 (2.3)	1 (0.5)
OOC	10 (2.9)	5 (3.9)	5 (2.3)
TC	23 (6.6)	7 (5.4)	16 (7.3)
TO	9 (2.6)	5 (3.9)	4 (1.8)
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
Glu	3.6 (1.2)	3.7 (2)	3.5 (1)
Blood Urea Nitogen (BUN)	3.7 (1.4)	3.9 (1.3)	3.6 (1.5)
Creatinine	87 (26)	86 (28.5)	88 (25.15)
Weight	54 (12)	55 (12.2)	54 (12)
Height	1.68 (0.13)	1.68 (0.11)	1.67 (0.14)
BMI	19.06 (3.96)	19.12 (3.67)	19.05 (4.02)

This is a descriptive table indicating the clinical presentations of the patients with TB and TB-DM comorbidity. It includes aspects such as HIV status, TB regimen, Smear results, outcome of treatment, BUN, Glucose, Height, and BMI.

Table 3
Univariate analysis for potential risk factors* in the TB and TB/DM patients.

	TB-DB (n = 129) n (%)	TB (n = 218) n (%)	p-value
Age categories			
Under 30	59 (45.74)	104 (47.71)	0.181
31–40	54 (41.9)	76 (34.9)	
41–50	9 (7)	31 (14.2)	
51–60	6 (4.7)	5 (2.3)	
Over 60	1 (0.8)	2 (0.9)	
Employed			
Yes	79 (61.2)	154 (70.6)	0.047
No	50 (38.8)	64 (29.4)	
Ever drank alcohol			
Missing data	0 (0)	1 (0.5)	0.153
NA	26 (20.2)	28 (12.8)	
No	53 (41.1)	84 (38.5)	
Yes	50 (38.8)	105 (48.2)	
No of cigarettes daily +			
Missing data	21 (60)	46 (71.9)	0.037
<20	9 (25.7)	15 (23.4)	
>20	5 (14.3)	3 (4.7)	
Household members			
<2persons	65 (50.4)	129 (59.2)	0.069
>2persons	64 (49.6)	89 (40.8)	
Regimen			
2RHZE/4RH	120 (93)	195 (89.4)	0.179
2SRHZE/1RHZE/5RHE	9 (7)	23 (10.6)	
Median (IQR) BUN	3.9 (1.3)	3.6 (1.5)	0.042

*Only variables significant at p value < 0.2 in the univariate analysis are listed.
+ based on the number of patients who ever smoked

Table 4
Logistic regression analysis of risk factors* for diabetes in TB patients.

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% EXP (B) Lower	C.Ifor Upper
Blood Urea Nitrogen (BUN)	.192	.095	4.050	1	.044	1.211	1.005	1.460
No of cigar-ettes > 20	−1.191	.593	4.031	1	.045	.304	.095	.972

Univariate chi-square test indicating that the regimens, employment status, ever taken alcohol, the number of cigarettes taken per day, age categories and the number of household members were associated with having or not having DM among TB patients at p-value < 0.2
*Only significant risk factors are listed

Table 5
Comparison of smear conversion time between diabetic and non-diabetic among TB patients.

	N	Mean	Median	Std. deviation	Std. error mean	p-value
Diabetic	108	3.2037	3.0	.65223	.06276	0.365
Non-diabetic	197	3.1421	3.0	.51518	.03671	

A comparison of the treatment time difference between patients who have diabetes and non-diabetic TB patients

the same for the two groups of patients.

Discussion

We had three main findings in our study. The prevalence of DM (HBA1C > 6%) among TB infected patients was 37.2%. Patients regimen, employment status, alcohol intake, smoking, age and household size were some of the factors associated with DM among TB patients at p-value < 0.200. The number of cigarettes smoked per day and the value of the BUN were significant risk factors of developing DM among TB patients as indicated in Table 4 which indicates that patients taking < 20 cigarettes a day are less likely to develop DM compared to those that take > 20 cigarettes a day (p values = 0.045) while a unit increase in BUN increases the odds of diabetes by 1.211 times. Though the mean time to conversion was slightly higher for the TB-DM patients compared to the TB patents, the difference was not statistically significant (p = 0.365) as indicated in Table 5.

Our finding doesn't vary significantly from other studies. In India, a population-based study conducted in six large cities from different regions estimated an age-standardized prevalence of type 2 diabetes among TB patients to be 39.1%. [21–23] Similarly, cross-sectional studies from have estimated DM prevalence among TB patients to be 15.6%, 18.27% and 38.6%, respectively with a prevalence of 15.8% in rural areas of Puducherry [24–27]. In the current study, the prevalence of DM in TB patients was found to be 37.2%. Thus, the prevalence of DM in TB patients in this study is much higher than the prevalence seen in the general population which range from 5.5% to 18.3% [14].

A higher prevalence study of 44% was reported from Kerala, India though it had used a different diagnostic criteria, i.e. measurement of HbA1c > 6.5% to diagnose diabetes [28,29]. The WHO-IUALTD collaborative framework suggests that the type of screening and diagnostic tests for DM in TB patients should be adapted to the context of local health systems and the availability of resources [30–32].Using similar diagnostic cut-off, studies from China and Indonesia have demonstrated a lower prevalence [33–35]. Study by Jain et al. reported a prevalence of impaired glucose tolerance (IGT) of 16.98% and they had used oral glucose tolerance test to diagnose IGT [36,37].

Patients regimen, employment status, alcohol intake, smoking, age and household size were found to be associated with DM among TB patients at p-value < 0.200. Other studies found family history to be a significant factor of predicting DM among TB patients [38–40].Similar to our study, cigarettes smoking have also been found to be associated with DM among TB patients [41–43]. In these studies the average duration of smoking among smokers was 15.1 ± 12.9 years while, two-thirds of males consume alcohol with an average daily consumption of 295 ± 75.9 ml per day. Other studies have also indicated age, family history of diabetes and consumption of alcohol as having significant association to DM.

We did not find any significant association between BMI and diabetes. Similar results have been reported by other studies [44–46]. Fewer studies have reported that patients with TB and DM are significantly underweight and have more weight loss [45,46]. Alisjahbana et al. reported a significantly higher median BMI in TB-DM patients when compared to non-diabetic TB patients [47]. We found out that there was a significant association between alcohol consumption and prevalence of diabetes among TB patients. This has not been stated elsewhere. It could be attributed to high alcohol intake in the area. We could not establish a significant association of diabetes with sputum positivity conversion despite most of the studies indicating the same [41–43].

Our study had some few limitations the sample size was small and limited to 2 counties from Nairobi and Kiambu with 7 randomly selected high TB burden health facilities Thus, further studies with a larger sample frame would enable the study to be more representative. Despite the limitations, our study is first to explore the Diabetes status among the newly diagnosed TB patients in the 2 counties among the high burden TB/DM to provide novel insights into the coexistence of TB and DM.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2018.04.005.

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