Transient Impact of Dysglycemia on Sputum Conversion among Smear-Positive Tuberculosis Patients in a Tertiary Care Facility in Ghana

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Ernest Yorke[1], Vincent Boima[1], Ida Dzifa Dey[1], Maame-Boatemaa Amissah-Arthur[1], Vincent Ganu[2], Ernest Amaning-Kwarteng[2], John Tetteh[1,2] and C. Charles Mate-Kole[1,2]

[1]University of Ghana, Accra, Greater Accra, Ghana. [2]Korle-Bu Teaching Hospital, Accra, Greater Accra, Ghana.

ABSTRACT

BACKGROUND: Apart from increasing the risk of tuberculosis (TB), diabetes may be associated with more severe disease and lower rates of sputum conversion among TB patients.

METHODS: We conducted a baseline cross-sectional study with a longitudinal follow-up of newly diagnosed smear-positive TB patients for 6 months. Sputum conversion rates between those with dysglycemia and those without were compared at 2 months (end of the intensive phase) and 6 months (end of the treatment). Descriptive statistics and logistic regression were computed to assess factors associated with dysglycemia as well as sputum conversion.

RESULTS: A significantly higher proportion of normoglycemic patients had negative sputum compared with those with dysglycemia (83% vs 67%, *P*-value < .05) at 2 months but not at 6 months (87% vs 77%, *P*-value > .05). After controlling for age group and adjusting for other covariates, patients with dysglycemia were 66% less likely to convert sputum than those with normoglycemia. Females were at least 7 times more likely than males and those with high waist-to-hip ratio (WHR) of 88% were less likely compared with those with low WHR for sputum conversion at 2 months, respectively. At 6 months, females (compared with males) and those with high WHR (compared with those with normal WHR) were at over 9 times increased odds and 89% less likely for sputum conversion, respectively.

CONCLUSION: A significantly lower proportion of smear-positive TB patients with dysglycemia converted to smear negative after 2 months of treatment but not at the end of the treatment, thus suggesting a transient impact of dysglycemia on sputum conversion.

KEYWORDS: Tuberculosis, smear Positive, dysglycemia, sputum Conversion, transient.

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CORRESPONDING AUTHOR: Ernest Yorke, Department of Medicine and Therapeutics, School of Medicine and Dentistry, College of Health Sciences, University of Ghana, P.O. Box GP 4236, Legon, Accra, Ghana. Email: pavlovium@yahoo.com

1. Introduction

Worldwide, tuberculosis (TB) infections are still high despite the many strategies to curtail it. In 2016, there were an estimated 10.4 million new TB cases worldwide with about 1.7 million people dying from it, making it the topmost infectious killer.[1] With the high global burden of diabetes and an increasing trend, especially in type 2 diabetes, the recognized reciprocal negative impact of TB and diabetes on each other is likely to worsen.[2–4] Diabetes represents a significant population risk for TB infections of ~1.5 to 7.8 times[5–8] and may also be related to the development of multidrug resistant TB with an odds ratio (OR) of 2.1.[9] Diabetes may be associated with more severe disease, higher rates of reactivation of old TB foci, more cavitations, and higher risk of death among TB patients.[6,9–11] The relationship between rates of sputum conversion among TB patients with diabetes or dysglycemia appears inconsistent.[9,12–16] Some studies have suggested a reduced rate at 2 months (end of the intensive phase) and 6 months (end of the treatment)[9,12] while others have shown no relationship between diabetes and sputum conversion rate at the end of the secondmonth.[14,17] More data are needed to help ascertain the impact of dysglycemia on the sputum conversion rate among TB patients. The additional information would help determine if adjustments must be made to the current treatment regime. Thus, the present study ascertained the impact of dysglycemia on sputum conversion among smear-positive TB patients in a tertiary care setting.

2. Materials and Methods

2.1 Study Design and Site

The study adopted a cross-sectional baseline assessment with a longitudinal follow-up for 6 months at the outpatient referral chest clinic of the Korle-Bu Teaching Hospital, which is a tertiary care facility in Ghana.

2.2 Participants and Sampling

We consecutively enrolled patients who were either first diagnosed at or referred to the Korle-Bu chest clinic as newly diagnosed smear-positive TB patients. Included patients were those aged 18 years or older, had no previous TB treatment, and who gave informed written consent. Patients who were diagnosed with smear-negative TB or extrapulmonary TB, those who had previously been treated for TB, or refused to give informed consent were excluded from the study.

Differences in sputum culture conversion rates comparing pulmonary TB patients with and without diabetes mellitus (DM) from previous studies have varied between zero and 15%.[18–22] Assuming a 15% difference in sputum conversion rates between pulmonary TB patients with or without DM, 134 smear-positive TB patients would be adequate to detect a difference in sputum conversion based on a power of 80% and a 2-sided confidence interval (CI) of 90%. Sampling was done on weekdays for 16 months until a sample size of 200 was obtained of which 171 had complete data. Anti-TB treatment regimen used included a combination of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) for the intensive phase (first 2 months) while only rifampicin (R) and isoniazid (H) were used in the continuation phase (next 4 months). None of the recruited participants admitted to being a known diabetic prior to the study.

The center employs the directly observed therapy strategy (DOTS) to improve compliance to treatment. Moreover, the TB control program employs treatment supporters to help patients adhere to their treatment in the community. They pay visits and assess compliance to treatment; challenges identified are remedied. This ensures a high rate of compliance to medications and successful treatment outcomes.

2.3 Measurements

Patients enrolled were given a data abstraction tool to capture data concerning their sociodemographic and anthropometric characteristics as well as medical history.

To assess their glycemia status, a 75 g oral glucose tolerance test (OGTT) was administered to all patients. A 10 mL fasting blood sample was taken into fluoridated blood sample tubes (kept on ice and centrifuged within 15 min of blood draw), ethylene-diamine-tetra-acetic acid (EDTA) tubes, and plain tubes.[23] Patients then received 75 g of glucose in 250 mL of water, and after–2-h blood sample was taken into fluoridated sample tubes and processed similarly as the fasting sample. Plasma glucose was determined using glucose oxidase commercial reagent kits and controls (Diasys GmBH, Germany). Diabetes was diagnosed when the fasting plasma glucose (FPG) and the 2-h postprandial (2HPP) blood glucose level were >7 mmol/L and >11.1 mmol/L, respectively, or on regular medication for diabetes. FPG and 2HPP values below 6.1 mmol/L and 7.8 mmol/L respectively are normal. Diagnoses of impaired or borderline fasting and glucose tolerance were made when FPG and 2HPP values were 6.1 to 6.9 mmol/L and 7.8 to 11 mmol/L, respectively.[24] None of the participants was known to have diabetes prior to enrollment. Patients found to have diabetes were referred to receive appropriate care.

The presence of *Mycobacterium tuberculosis* (MTB) was tested using the Cepheid GeneXpert system, a rapid, nucleic acid amplification test (NAAT) through polymerase chain reaction to confirm the diagnosis. Sputum smear microscopy using Ziehl–Neelsen staining was however used to ascertain sputum conversion at 2 months (end of the intensive phase) and 6 months (end of the treatment). The sputum conversion rate was determined as the percent of enrolled smear-positive pulmonary TB cases that converted to smear-negative status at 2 months and 6 months. For the purposes of analyses, participants with "very low" and "low" detected MTB and those with "medium" and "high" detected MTB by GeneXpert were recategorized as low and high loads, respectively.

Body mass index (BMI) was calculated and categorized as obese, overweight, normal, and underweight based on the cut-offs of 30.0 or more, 25 to 29.9, 18.5 to 24.9, and <18.5 (kg/m^2), respectively.[25]

2.4 Statistical Analysis

Data were analyzed with the statistical software Stata version 15 after initial capture with Microsoft Excel 2010. Analyses for the various characteristics were performed for patients with complete data. For the purposes of analyses, patients were categorized as either dysglycemia or abnormal (impaired glucose tolerance and diabetes) or normal using 2HPP values. Sociodemographic, anthropometric, and clinical variables were summarized and compared between these two groups using the χ^2 test. A similar analysis using FPG was not performed due to the very few numbers involved.

Two approaches of statistical analysis were performed involving the descriptive χ^2 test and logistic regression analysis. Descriptive cross-tabulation analysis was performed to assess covariates significantly associated with 2HPP using the χ^2 test. Due to the dummy nature of our study outcomes, a binary logistic regression model was used to test the effect of sociodemographic, clinical, and lifestyle factors on 2HPP and sputum conversion separately. Logistic regression analysis was conducted to estimate factors significantly influencing 2HPP. Age group as the only significant factor influencing 2HPP was controlled and other covariates were adjusted in further analysis to quantify the impact of 2HPP on sputum conversion for 2 months and 6 months separately by adopting logistic regression. The statistical tests were set at the 5% significance level.

3. Results

3.1 Participant Characteristics

The ages of the participants were evenly distributed across the age groups with a mean age of 38.2 ± 13.6 years (range 18–75 years). The majority of participants (74.8%) were educated up to senior high/ordinary level (SHS/O level) and 68.2% were underweight. Males represented 78.9% of the study participants. The test of association suggests that 2HPP is associated with only age group and educational level (P-value < .05). The result shows that generally, the proportion of participants with abnormal 2HPP increases with age, the highest seen among the middle-age group 45 to 54 (54.5%). Also, the proportion of participants with dysglycemia with a low sputum load was 19.4% compared to 20% in the case of normoglycemic patients whereas 80.6% and 79.8% of participants with high sputum load were dysglycemic and normoglycemic, respectively. These marginal differences did not show any significant differences. Full details of the demographic characteristics are shown in Table 1.

3.2 Glycemic Variables of Participants

Of a total of 171 participants, using FPG values 87.1%, 8.8%, and 4.1% had normal glucose, impaired fasting, and diabetes, respectively. Using 2HPP values, 61.4%, 27.5%, and 11.1% had normal glucose, impaired glucose tolerance, and diabetes, respectively. The combined prevalence of dysglycemia was thus 12.9% ($n = 22$) and 38.6% ($n = 66$) using fasting glucose and 2HPP values, respectively, as shown in Table 2.

3.3 Predictors of Abnormal Glucose Patterns Among Study Participants

Factors influencing the development of abnormal glucose were explored using binary logistic regression. Being aged 45 to 54 years had 6.43 increased odds (P-value = .007) for developing abnormal glucose compared to the reference age of 18 to 24 years. There were no other significant predictors of abnormal glucose values as shown in Table 3.

3.4 Comparison of Sputum Conversion Rates at 2 and 6 Months

The sputum status was assessed and compared to determine the sputum conversion rates at 2 and 6 months. At 2 months, a significantly higher proportion of normoglycemic subjects had negative sputum compared with those with dysglycemia (83% vs 67%) (Z-test = −2.5; $P < .05$). Despite the proportionally higher numbers of the dysglycemia group that maintained sputum conversion at 6 months, there was no statistical difference between the 2 groups (87% vs 77%, Z-test = −1.71, $P > .05$), as shown in Table 4.

Table 1. Sociodemographic, lifestyle, and clinical characteristics associated with 2HPP among TB patients

	2HPP CATEGORY			
	ABNORMAL	NORMAL	TOTAL	
DEMOGRAPHIC CHARACTERISTICS	*N* (%)	*N* (%)	*N*	χ^2
Age group (years)			171	**10.29***
18 to 24	8 (22.2)	28 (77.8)	36	
25 to 34	13 (31.0)	29 (69.0)	42	
35 to 44	15 (48.4)	16 (51.6)	31	
45 to 54	18 (54.5)	15 (45.5)	33	
55 to 64	13 (44.8)	16 (55.2)	29	
Sex			171	**0.65**
Male	55 (40.7)	80 (59.3)	135	
Female	12 (33.3)	24 (66.7)	36	
Marital status			171	**1.24**
Married	30 (40.0)	45(60.0)	75	
Single	32 (36.8)	55 (63.2)	87	
Separated/divorced	5 (55.6)	4 (44.4)	9	
Educational level			171	**9.65***
None	5 (33.3)	10 (66.7)	15	
Primary	6 (37.5)	10 (62.5)	16	
Middle/JHS	34 (54.0)	29 (46.0)	63	
SHS/O level	14 (28.6)	35 (71.4)	49	
Tertiary	8 (28.6)	20 (71.4)	28	
Employment status			170	**1.79**
No	13 (30.2)	30 (69.8)	43	
Yes	53 (41.7)	74 (58.3)	127	
Smoking status			168	**0.08**
Yes	5 (35.7)	9 (64.3)	14	
No	61 (39.6)	93 (60.4)	154	
Alcohol intake			167	**0.77**
Yes	9 (32.1)	19 (67.9)	28	
No	57 (41.0)	82 (59.0)	139	
BMI			157	**1.78**
Below 18.5 (underweight)	45(42.1)	62 (57.9)	107	
18.5 to 24.9(normal)	15 (33.3)	30 (66.7)	45	
25 to 29.9 (overweight)	1 (20.0)	4 (80.0)	5	
Systolic BP			170	**0.88**

(continued)

Table 1. Continued.

DEMOGRAPHIC CHARACTERISTICS	2HPP CATEGORY ABNORMAL *N* (%)	NORMAL *N* (%)	TOTAL *N*	χ^2
Normal	43 (39.8)	65 (60.2)	108	
Elevated	16 (34.0)	31 (66.0)	47	
Hypertension	7 (46.7)	8 (53.3)	15	
Diastolic BP			170	**0.21**
Normal	59 (39.3)	91 (60.7)	150	
Elevated	5 (33.3)	10 (66.7)	15	
Hypertension	2 (40.0)	3 (60.0)	5	
Waist–hip ratio			171	**0.28**
Low	55 (40.1)	82 (59.9)	137	
Moderate	5 (35.7)	9 (64.3)	14	
High	7 (35.0)	13 (65.0)	20	
Sputum load (2HPP)			171	**0.016**
Low Load	13 (19.4)	21 (20.2)	34	
High Load	54 (80.6)	83 (79.8)	137	

*$P < .05$.
Abbreviations: 2HPP, 2-hour post-prandial glucose; TB, tuberculosis; BP, blood pressure; BMI, body mass index; SHS, senior high school;

3.5 *Predictors of Sputum Conversion at 2 and 6 Months*

Binary logistic regression models were used to test the effect of sociodemographic, clinical, and lifestyle factors on the treatment (sputum conversion) (Table 5). After controlling for demographic factors and adjusting for age groups, the following

Table 2. Glycaemic variables of study participants

VARIABLE	FREQUENCY (*N*)	PROPORTION (%)
Fasting Plasma Glucose (mmol/L)		
(Mean ± *SD*)	5.21 ± 1.46	
Normal (<6.1)	149	87.1
Impaired/borderline (6.1–7)	15	8.8
Diabetes (>7.1)	7	4.1
2 HPP Glucose (mmol/L)		
(Mean ± *SD*)	8.24 ± 3.26	
Normal (<6.1)	105	61.4
Impaired/borderline (6.1–7)	47	27.5
Diabetes (>7.1)	19	11.1

Abbreviation: 2-HPP, 2-hour post-prandial glucose.

Table 3. Factors influencing abnormal glycaemia among TB patients

COVARIATES	AOR	*P*-VALUE	95% CONF. INTERVAL LOWER	UPPER
Age group				
18 to 24	**Ref**			
25 to 34	1.66	.398	0.51	5.38
35 to 44	3.27	.076	0.88	12.12
45 to 54	6.43	.007*	1.66	24.86
55 to 64	2.90	.144	0.70	12.11
Sex				
Male	**Ref**			
Female	0.80	.767	0.18	3.50
Marital status				
Married	**Ref**			
Single	1.34	.504	0.57	3.19
Separated/divorced	1.10	.900	0.24	5.07
Educational level				
None	**Ref**			
Primary	1.66	.586	0.27	10.26
Middle/Junior High School	3.25	.125	0.72	14.68
Senior High School/O-level	1.08	.926	0.22	5.18
Tertiary	1.02	.977	0.20	5.30
Employment status				
No	**Ref**			
Yes	2.26	.052	0.99	5.14
Smoking status				
Yes	**Ref**			
No	0.59	.460	0.14	2.40
Alcohol intake				
Yes	**Ref**			
No	0.56	.299	0.18	1.68
Systolic BP				
Normal	**Ref**			
Elevated	1.05	.901	0.47	2.37
Hypertension	1.41	.663	0.30	6.61
Diastolic BP				
Normal	**Ref**			

(continued)

Table 3. Continued.

COVARIATES	AOR	*P*-VALUE	95% CONF. INTERVAL LOWER	UPPER
Elevated	0.42	.250	0.09	1.86
Hypertension	0.49	.517	0.06	4.26
Waist-to-hip ratio				
Low	**Ref**			
Moderate	0.98	.978	0.18	5.17
High	0.90	.900	0.19	4.39

*$P < .05$.
Abbreviations: aOR, adjusted odds ratio; TB, tuberculosis; SHS/O level, senior high school/ordinary level.

Table 4. Test of proportion showing the differences in negative sputum test result between TB patients subjects with abnormal glucose and those with normal glucose (using 2HPP) at two and six months ($n = 171$)

2 HPP	2 MONTHS PROPORTION (95% CI)	6 MONTHS PROPORTION (95% CI)
Abnormal	67.16 (55.92–78.41)	77.61 (67.63–87.59)
Normal	83.65 (76.55–90.76)	87.5 (81.14–93.85)
***Z*-statistic**	**−2.51***	**−1.71**

**P*-value < .05.
Abbreviations: 2HPP, 2-hour post-prandial glucose; TB, tuberculosis

factors were associated with sputum conversion at 2 months: subjects with dysglycemia were 66% less likely than those with normoglycemia (OR (adjusted odds ratio (aOR)), [95% confidence interval (CI)], *P*-value: 0.34, [0.14–0.82], .018); females were 7.44 times more likely than men (aOR, [95% CI], *P*-value: 7.44, [1.73–32.0], .007); and those with high WHR were 88% less likely compared with those with low WHR (aOR, [95% CI], *P*-value: 0.12, [0.02–0.54], .006) to convert sputum, respectively. At 6 months and after similar adjustments, females (compared with males) and high WHR (compared with those with normal WHR) were 9.29 times more likely (aOR, [95% CI], *P*-value: 7.44, 9.29 [1.78–48.5], .008] and 89% less likely (aOR, [95% CI], *P*-value: 0.11, [0.02–0.63], .013) for sputum conversion, respectively.

4. Discussion

The results of the study show that at 2 months, a significantly higher proportion of normoglycemic subjects had negative sputum compared with those with dysglycemia. However,

Table 5. 2HPP influence on treatment outcome (sputum conversion) among TB patients adjusting for demographic factors and controlling for age group

Covariates	PERIOD OF TREATMENT OUTCOME 2 MONTHS AOR (95% CI) *P*-VALUE	6 MONTHS AOR (95% CI) *P*-VALUE
Two HPP		
Normal	**Ref**	**Ref**
Abnormal	0.34 (0.14–0.82) .018	0.46 (0.17–1.25) .128
Sex		
Male	**Ref**	**Ref**
Female	7.44 (1.73–32.0) .007	9.29 (1.78–48.5) .008
Marital status		
Married	**Ref**	**Ref**
Single	1.47 (0.64–to 3.41) .363	1.75 (0.06–4.52) .249
Separated/ divorced	0.41 (0.08–1.91) .254	0.42 (0.06–2.81) .369
Educational level		
None	**Ref**	**Ref**
Primary	0.44 (0.08–2.49) .358	0.74 (0.08–6.46] .785
Middle/Junior High School	1.19 [(0.25–5.36) .826	3.82 (0.57–25.52) .166
Senior High School/O-level	0.84 (0.18–3.82) .819	2.00 (0.33–12.14) .453
Tertiary	0.72 (0.15–3.37) .679	0.72 (0.13–4.04) .713
Employment status		
No	**Ref**	**Ref**
Yes	1.27 (0.50–3.21) .619	0.22 (0.04–1.14) .072
Smoking status		
Yes	**Ref**	**Ref**
No	0.49 (0.08–2.91) .435	1.94 (0.31–12.27) .482
Alcohol intake		
Yes	**Ref**	**Ref**
No	1.67 (0.50–5.58) .401	2.21 (0.26–5.57) .809
Waist-to-hip ratio		
Low	**Ref**	**Ref**
Moderate	0.48 (0.09–2.44) .374	0.81 (0.11–5.95) .837
High	0.12 (0.02–0054) .006	0.11 (0.02–0.63) .013

Abbreviations: 2HPP, 2-hour post-prandial glucose; aOR, adjusted odds ratio; SHS, senior high school TB, tuberculosis

despite the proportionally higher numbers of the normoglycemia group that maintained sputum conversion at 6 months, there was no statistical difference between the 2 groups. This suggests a transient impact of dysglycemia on sputum conversion among TB patients. While some studies have supported the negative impact of diabetes on sputum conversion throughout the period of TB treatment, others have showed a transient impact.[9,11,12] Alisjahbana *et al.* reported that TB patients who were diabetic had significantly higher percent of smear-positive results than their nondiabetic counterparts at 2 months (18.1% vs 10.0%). Unlike our study, after 6 months (end of the treatment), 22.2% of sputum specimens from diabetic patients were positive for *M tuberculosis* (aOR, 7.65; $P = .004$).[9] In a retrospective study that assessed TB patients with self-reported diabetes from south Texas (USA) and north-eastern Mexico, the authors reported that TB patients were more likely to remain positive at the end of the first (Texas cohort) or second (Mexico cohort) month of treatment,[12] which was similar to our study. A systematic review published in 2011 by Baker *et al.* reported an increased risk of relapse in these patients (relative risk, 3.89; 95% CI, 2.43–6.23). Unlike our study, some studies have however shown no relationship between diabetes and sputum conversion rate at the end of month 2,[13,16,17] while a trend toward increased time to sputum conversion has rather been found in other studies.[15,26,27]

The transient impact of dysglycemia on sputum conversion rate suggests possible nonlasting pathophysiological linkages and putative mechanisms.[28,29] The risk of TB patients with diabetes for reduced sputum conversion rate is suggested putatively due to the reduced numbers as well as the function of T lymphocytes involved in T-helper cells 1(TH1) cytokine inhibition of *M tuberculosis*.[30,31] In diabetes, dysfunction of macrophages occurs, which impairs phagocytic and chemotactic function as well as the production of reactive oxygen species.[30,31] Further, the impairment of chemotaxis of monocytes is thought to occur in diabetes.[32] The respiratory burst used in expelling pathogens is also thought to be impaired with diabetes.[30,31]

TB on its own has been linked to the development of impaired glucose tolerance (IGT)[28,33] and new-onset diabetes.[28,34] While IGT generally normalizes after TB has been treated, the risk of developing type 2 diabetes in the future remains high.[35] Some other studies revealed that between 19% to 42.6% of active TB patients, who were discovered to have IGT or diabetes, had significant reduction or complete regression in the rates after treatment.[28,29] This suggested stress response to infection leading to dysglycemia is thought to be due to the elaboration of interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha.[5,35]

Unsurprisingly in our study, most participants were young, male, and single; those are well-known sociodemographic characteristics of TB patients.[1,36,37] Other risk factors for TB include low incomes, the load of the bacilli, malnutrition, excessive alcohol use, overcrowding, smoking, HIV infection, diabetes, drugs that cause immunosuppression, and closeness to a person with active TB.[1,5–36]

The increased risk of the age group 45–54 years with abnormal blood glucose (aOR, 6.43) may represent an increased inherent risk for dysglycemia and type 2 diabetes conferred by increasing age.[38] Subjects with high WHR were less likely to convert sputum compared with those with normal WHR both at 2 and 6 months. High WHR is a risk factor for dysglemia and diabetes,[39] which influences the development of reduced clearance of TB pathogens as described earlier on.[30,31] This association is also independent of age, family history of diabetes, and sex;[39] the sex association is stronger in women than men.[39] Central obesity as measured by parameters such as WHR, waist circumference (WC), and BMI has been associated with impaired glucose–insulin homeostasis and insulin clearance, decreased insulin-stimulated glucose disposal finally which leads to decreased glucose tolerance.[40]

It is not clear why females were more likely to convert sputum than male counterparts both at 2 and 6 months. It must, however, be stated that females are more likely than men to be compliant with their treatment and also keep their appointments, which may in turn improve treatment outcomes.[41,42]

5. Conclusion

This study has added to the body of knowledge on the impact of dysglycemia on sputum conversion among TB patients. A significantly lower proportion of smear-positive TB patients with dysglycemia converted to smear negative after 2 months of treatment but not at the end of treatment suggesting a transient impact of dysglycemia on sputum conversion. Other factors, including age, female sex, and increased WHR, have shown association. Larger studies are needed to validate these findings. A change in the current TB regimen is not recommended based on our findings.

Future research is required in this field and must compare the severity of TB presentation between the dysglycemia and normoglycemic groups, such as symptom burden, pattern of lobe involvement, reactivation of old foci, rates of hemoptysis, fever, and atypical presentations and cavitations. We plan to perform formal glucose tolerance tests at 2 months (end of the intensive phase) and at 6 months (end of the treatment) to confirm whether dysglycemia associated with TB is transient. Patients would also be followed up to ascertain the RRs between the two groups.

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The data that support the findings of this study are available from the corresponding author upon request

Author Contributions

EY conceived the study, participated in its design, data collection, analysis, and drafted the manuscript and collation of all drafts. VB, IDD, VG, MBAM, EKA, JT, and CCM contributed to the study design, data collection, analysis, and writing the manuscript draft. All authors read and approved the final version of the manuscript.

Ethical Approval and Consent to Participate

Ethical and Protocol approval for the study was sought from the College of Health Sciences Ethics and Protocol Review Committee of the University of Ghana with reference number URF/9/ILG-076/2015 to 2016. It complied with the Helsinki Declaration of 1964 (Revised 2013) on human experimentation. All patients provided written informed consent. Strict confidentiality of data and privacy for study participants were ensured. Data were kept secured and available only to the principal investigator.

ORCID iD

Ernest Yorke https://orcid.org/0000-0003-4257-7492

Trial Registration

Not applicable, as no trial was conducted.

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Author Biography

Ernest Yorke, FWACP, FGCP, MSc, Diabetes (Cardiff), MSc, Endo. (UK), MB ChB, BSc, Cert. HAM (Ghana Institute of Management and Public Administration, GIMPA). Dr Ernest Yorke is a fellow of the West African College of Physicians and the Ghana College of Physicians & Surgeons. Currently, he is a senior lecturer at the University of Ghana Medicine School, and a consultant physician/endocrinologist at the Korle-Bu Teaching Hospital, Accra. He also holds double Masters' degrees from universities from the United Kingdom. He has been extensively involved in the organization and also served as a facilitator to numerous metabolic and cardiovascular Continuing Medical Education programs, both locally and abroad. He values the use of practical tools as well as new technology in research and development to solve problems and also to advance knowledge. He has served as a consultant and Advisory Board member for a number of multinational pharmaceutical companies involved in diabetes care, both locally and abroad. His main research interests include diabetes and kidney disease, psychological impact of diabetes, pregnancy outcomes in diabetes, and diabetic foot care as well as thyroid diseases. He has over 30 peer-reviewed publications to his credit. He has other interests outside clinical work and academia. Among many other volunteer works, he is currently the Chairman of the Greater Accra Division of the Ghana Medical Association and also a Board member of Diabetes Youth Care, a non-governmental organization dedicated to the care and well-being of young people living with diabetes in Ghana. He is married with three children and watches TV in his spare time.