Annals of Medical Laboratory Science (2021) **1**(2): 50 - 58
https://www.annalsmls.org
https://doi.org/10.51374/annalsmls.2021.1.2.0042

Hyperglycaemia in newly diagnosed pulmonary tuberculosis patients: a cross-sectional study of the Agona District Hospital

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How to cite this paper: Ephraim, R.K.D., Baah, S.K., Sakyi, S.A., Darkwah, K.O., and Abaka-Yawson, A. (2021) Hyperglycaemia in newly diagnosed pulmonary tuberculosis patients: a cross-sectional study of the Agona District Hospital. *Annals of Medical Laboratory Science 1(2): 50 - 58*

Received: October 17, 2020
Accepted: May 10, 2021
Published: June 20, 2021

ABSTRACT

Background: Diabetes mellitus is an important risk factor associated with tuberculosis (TB). This study investigated the prevalence and determinants of hyperglycemia among newly diagnosed pulmonary tuberculosis patients in the Agona Swedru Municipality.

Method: A hospital-based cross-sectional study was conducted from December 2015 to April 2016. One hundred (100) newly diagnosed pulmonary tuberculosis patients at the Agona Swedru Municipal Hospital (ASMH) were enrolled for the study. Socio-demographic, clinical and anthropometric measurements were collected and fasting blood glucose (FBG) measured using standard protocols. Data was analyzed using Statistical Package for Social Sciences (SPSS) software version 20.0.

Result: Of the 100 participants, 26% had hyperglycemia. The significant factors associated with increased risk of hyperglycemia among participants were history of diabetes mellitus (OR = 8.17, p= 0.004), severity of infection (OR = 23.64, p < 0.001) and duration of symptoms (OR= 2.63, p= 0.042).

Conclusion: Hyperglycemia was common among newly diagnosed pulmonary tuberculosis patients. History of diabetes mellitus, severity of infection, and duration of symptoms were the determinants of hyperglycemia in pulmonary tuberculosis. Regular screening of hyperglycemia is essential in the management of tuberculosis. Finally, further studies should be conducted on glucose levels among pulmonary tuberculosis patients using higher sample size to increase the understanding of the subject.

Annals of Medical Laboratory Science (2021) 1(2), 50 - 58

Keywords: Pulmonary tuberculosis; hyperglycemia; fasting blood glucose, determinants

INTRODUCTION

Pulmonary tuberculosis (PTB) is a specific infectious disease caused by *Mycobacterium tuberculosis*. The disease is normally chronic with cardinal symptoms like persistent cough with or without expectoration, intermittent fever, loss of appetite, weight loss, chest pain and haemoptysis (Shetty *et al.*, 2006). PTB can lead to an infection-related hyperglycemia which may mimic diabetes mellitus (DM). The hyperglycemia associated with PTB often aggravates the glycemic control of diabetes mellitus patients (García-Elorriaga and Del Rey-Pineda, 2014).

Currently, both PTB and DM are of great public health importance especially in Sub-Saharan Africa due to the congregating epidemics of both communicable and non-communicable diseases (Abate and Chandalia, 2003). According to the World Health Organization (WHO), there were an estimated 8.7 million incident cases of PTB and 1.4

https://doi.org/10.51374/annalsmls.2021.1.2.0042

million deaths from PTB in 2011 (Elhadd *et al.*, 2007). The International Diabetes Federation (IDF) also reported that more than 371 million people all over the world had DM and 471 billion USD was spent treating diabetes mellitus in 2012 (Viswanathan *et al.*, 2012).

Pulmonary tuberculosis may lead to the development of new DM cases (Del Prato *et al.*, 2007; Dooley and Chaisson, 2009). Studies have shown a high prevalence of DM and impaired glucose tolerance, in patients with PTB (Sen *et al.*, 2009). Impaired glucose tolerance is a significant risk factor for developing DM. In most of these cases, the impaired glucose tolerance relapses back to normal after successful treatment for PTB, however the increased risk of developing DM continues (García-Elorriaga and Del Rey-Pineda, 2014). As an infectious disease, PTB increases insulin resistance and stress-induced hyperglycemia (Ottmani *et al.,* 2010). Reactionary hyperglycemia often complements chronic infections like PTB due to the augmented pro-inflammatory state and release of counter regulatory stress hormones like epinephrine, cortisol and glucagon that are antagonistic of insulin (Webb *et al.,* 2009). Rifampicin, a very potent anti PTB drug has also been shown to induce a transient early phase hyperglycemia owing to augmentation of intestinal glucose absorption (Kibirige *et al.*, 2013).

Also, PTB is a known cause of pancreatitis (Niazi and Kalra, 2012) and PTB pancreatitis might reveal itself only after the development of diabetes mellitus. Even though a part of the hyperglycemia associated with PTB may be ascribed to the severe stress associated with the infection itself, the major factor in this process is hypofunction of the pancreas (Niazi and Kalra, 2012; García-Elorriaga and Del Rey-Pineda, 2014). There is dearth of data on hyperglycemia in infected PTB patients in Ghana and Africa. This study investigated the prevalence and determinants of hyperglycemia among newly diagnosed pulmonary tuberculosis patients in the Agona Swedru Municipality.

MATERIALS AND METHODS

Study design/site

This hospital based cross -sectional study was conducted among newly diagnosed PTB patients who attend the Agona Swedru Municipal Hospital (ASMH) in the Central Region of Ghana. ASMH is the main referral facility in the Agona municipality and its environs and provides services in obstetrics and gynecology, surgery, pediatrics and general medicine. It has a diabetes clinic which is scheduled twice in a week.

Study population/Eligibility criteria

We conveniently recruited 100 newly diagnosed pulmonary tuberculosis patients who visited the out-patient department of the Agona Swedru Municipal Hospital. Newly diagnosed PTB patients who attended the ASMH from December 2015 to April 2016 were included. Also, the study sealed off newly diagnosed and patients already with pulmonary tuberculosis who were on therapies (eg. metformin) and other complications (eg. Diabetes mellitus, HIV/AIDS) that affect glucose metabolism. Patients with other chronic ailments like liver disease and kidney disease were excluded.

Sample Size Determination

The sample size was determined from a Ghanaian study by Asante-Poku *et al.*, (2019) to be 9.4%. The prevalence rate from that study was used to calculate the sample size to be 131. After recruitment, 9 participants could not provide fasting samples. Also, 22 participants were excluded due to incomplete data. The final sample size was 100 as illustrated below using Fisher's sampling formula;

$$N = \frac{Z^2 P(1-P)}{D^2}$$

Where; N represents the estimated sample size
Z represents the constant for 95% confidence interval given as 1.96
P represents the prevalence of tuberculosis-diabetes co-morbidity of 9.4% obtained from a Ghanaian study
D represents the percentage margin of error taken as 5%

https://doi.org/10.51374/annalsmls.2021.1.2.0042

$$N = \frac{1.96^2 * 0.094 * 0.906}{0.05^2}$$

N = 131
Final Sample Size = 131 – 31 = 100

Ethical consideration
The participation of the respondents who are all native Ghanaians was voluntary and written informed consent was obtained from each of them. The study was approved by the University of Cape Coast Institutional Review Board (UCCIRB). Also, consent was sought from the Department of Medical Laboratory Technology and the ASMH authorities.

Data collection
An open-ended questionnaire was designed to capture precise information regarding their socio-demographic and clinical characteristics (e.g., age, sex, occupation, duration and level of PTB infection, polydipsia, polyuria, headaches and fatigue). Height (to the nearest meter) and weight (to the nearest 0.1 kg) in light clothing were measure using a wall-mounted graduated ruler and weighing balance (Seca, Hamburg, Deutschland) respectively. The body mass index (BMI) was then calculated as the ratio of the weight (kg) to the square of the height (m^2). BMI of less than 18.5, 18.5-24.9, 25-29.9, and ≥30 were classified as underweight, normal, overweight and obese respectively (Nuttall, 2015).

Sample collection and biochemical analysis
Sputum was obtained from the consented participants and PTB diagnosis was done with GeneXpert. Fasting venous blood (4 ml) was collected from participants into fluoride-oxalate tubes before administration of anti-tuberculous drugs. The tubes were centrifuged at 1500 revolutions per minute (rpm) for 15 minutes and plasma separated into test tube and stored at 2 ºC to 8 ºC until assayed. Fasting blood glucose (FBG) levels were estimated using the glucose oxidase/ peroxidase method (Barham and Trinder, 1972). Hyperglycaemia was defined as FBG greater than or equal to 6.4 mmol/l. Polyuria was also defined as passage of urine exceeding 3 litres a day whilst polydipsia was defined as excessive drinking of water.

Statistical analysis
Data was analyzed using Statistical Package for Social Sciences (SPSS) software version 20.0. Continuous variables were expressed as mean ± SEM, while categorical variables were expressed as proportion. Comparison of means was done by the Independent "t" test. Pearson product moment correlation was performed to determine the relationship between variables and to identify independent factors associated with the glucose levels of the participants under investigation. Multivariate logistic regression was done to determine the risk factors in the newly-diagnosed PTB patients and $P < 0.05$ was interpreted as statistically significant.

RESULTS
As shown in Table 1, the mean ages of the study participants were similar (P=0.135). More males 16 (88.9%) were within the age group of 60-69 and 13 (50.0%) females in the age group 30-39 (P=0.061). Also, majority of the males 60 (71.4%) were involved in informal occupation compared to the females 24 (28.6%). The mean body mass index (BMI) participants were similar (P=0.976). Symptoms of pulmonary tuberculosis (PTB) (P=0.463), duration of symptoms (P=0.900), severity of PTB (P=0.400), and duration after diagnosis of PTB (P=0.948) were similar in the participants.

The mean fasting blood glucose (FBG) was higher in the males (5.81 ± 1.48) than the females (5.62 ± 1.02) but the difference was not significant (P=0.516). With regards to hyperglycemia, 18 (66.7%) were males whilst 9 (33.3%) were females (P> 0.05). The difference between the males and the females regarding frequency of polyuria was significant (P=0.008) (Table 2).

As shown Table 3, hyperglycemia, timing of urination, frequency of polydipsia, timing of

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Table 1: Demographics and associated characteristics of newly diagnosed pulmonary tuberculosis patients

Characteristics	Male (n=69)	Female (n=31)	Total (n = 100)	P-value
Age (years)	44.45 ± 16.04	35.42 ± 17.68	41.65 ± 17.00	0.135
Age group n (%)				0.061
<20	3 (50.0)	3 (50.0)	6 (6.0)	
20-29	12 (54.5)	10 (45.5)	22 (22.0)	
30-39	13 (50.0)	13 (50.0)	26 (26.0)	
40-49	10 (100)	0 (0.0)	10 (10.0	
50-59	13 (100)	0 (0.0)	13 (13.0)	
60-69	16 (88.9)	2 (11.1)	18 (18.0)	
≥ 70	2 (40.0)	3 (60.0)	5 (5.0)	
Occupation n (%)				0.229
Informal	60 (71.4)	24 (28.6)	84 (84.0)	
Formal	9 (56.2)	7 (43.8)	16 (16.0)	
BMI (Kg/m2)	20.73 ± 3.78	20.71 ± 2.40	20.73 ± 3.40	0.976
BMI n (%)				0.696
Underweight	9 (64.3)	5 (35.7)	14 (14.0)	
Normal	55 (68.8)	25 (31.2)	80 (80.0)	
Overweight	5 (83.3)	1 (16.7)	6 (6.0)	
Symptoms of PTB n (%)				0.463
Dry cough	44 (62.0)	27 (38.0)	71 (71.0)	
Productive cough	54 (74.0)	19 (26.0)	73 (73.0)	
Cough with blood	9 (56.2)	7 (43.8)	16 (16.0)	
Shortness of breath	31 (62.0)	19 (38.0)	50 (50.0)	
Fever/night sweats	39 (65.0)	21 (35.0)	60 (60.0)	
Duration of symptoms (months)				0.900
< 5	44 (69.8)	19 (30.2)	63 (63.0)	
5-10	22 (68.8)	10 (31.2)	32 (32.0)	
>10	3 (60.0)	2 (40.0)	5 (5.0)	
Severity of PTB n (%)				0.400
Mild	36 (66.7)	18 (33.3)	54 (54.0)	
Moderate	17 (81.0)	4 (19.0)	21 (21.0)	
Severe	16 (64.0)	9 (36.0)	25 (25.0)	
Duration after diagnosis of PTB (Weeks)				0.948
< 5	56 (69.1)	25 (30.9)	81 (81.0)	
5-10.	10 (66.7)	5 (33.3)	15 (15.0)	
>10	3 (75.0)	1 (25.0)	4 (4.0)	

Data presented as frequency (percent). Categorical variable compared using Chi-Square Test. Parametric data compared using Student t-test; p-value <0.05 considered statistically significant. BMI = Body Mass Index, PTB = Pulmonary Tuberculosis, FBG = Fasting Blood Glucose, DOS = Duration of Symptoms, DPTB = Duration after diagnosis of PTB

polydipsia, increased significantly with increasing severity of PTB infection (P<0.001).

Table 4 shows the correlation between severity of PTB with FBG, BMI, duration of symptoms duration after diagnosis of PTB. PTB severity had a correlation with FBG (r=0.490, P<0.001), duration of symptoms (DOS) (r=0.505, P<0.001) and duration after diagnosis of pulmonary tuberculosis (DPTB) (r=0.332, P=0.001). Age had a correlation with BMI (r=0.515, P<0.001) and DOS (r=0.219, P=0.029). On the other hand, FBG had a correlation with BMI (r=0.211, P=0.035). BMI had a correlation with DPTB (r=0.201, P=0.045) while DOS also had a correlation with DPTB (r=0.395, P<0.001).

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Table 2: Hyperglycemia and diabetes mellitus associated characteristics among newly diagnosed PTB patients in relation to gender

Characteristics	Male	Female	Total	p-value
FBG (mmol/L)	5.81 ± 1.48	5.62 ± 1.02	5.75 ± 1.35	0.516
FBG n (%)				0.759
≤ 6.4	51 (69.9)	22 (30.1)	73 (73.0)	
> 6.4	18 (66.7)	9 (33.3)	27 (27.0)	
Symptoms of Hyperglycemia				0.977
Headache	36 (63.2)	21 (36.8)	57 (57.0)	
Fatigue	22 (62.9)	13 (37.1)	35 (65)	
History of diabetes				0.943
Yes	7 (70.0)	3 (30.0)	10 (10.0)	
No	62 (68.9)	28 (31.1)	90 (90.0)	
Polyuria				0.748
Yes	31 (67.4)	15 (32.6)	46 (46.0)	
No	38 (70.4)	16 (29.6)	54 (54.0)	
Frequency of Polyuria (Daily)				**0.008**
< 5 times	12 (46.2)	14 (53.8)	26 (26.0)	
5-10 times	53 (75.7)	17 (24.3)	70 (70.0)	
>10 times	4 (100)	0 (0.0)	4 (4.0)	
Timing of urination				0.805
Before Cough	33 (70.2)	14 (29.8)	47 (47.0)	
After Cough	36 (67.9)	17 (32.1)	53 (53.0)	
Polydipsia				0.428
Yes	41 (66.1)	21 (33.9)	62 (62.0)	
No	28 (73.7)	10 (26.3)	38 (38.0)	
Frequency of Polydipsia (Daily)				0.147
< 5 times	12 (60.0)	8 (40.0)	20 (20.0)	
5-10 times	54 (74.0)	19 (26.0)	73 (73.0)	
>10 times	3 (42.9)	4 (57.1)	7 (7.0)	
Timing of Polydipsia				0.344
Before Cough	36 (73.5)	13 (26.5)	49 (49.0)	
After Cough	33 (64.7)	18 (35.3)	51 (51.0)	

Data presented as frequency (percent). Categorical variable compared using Chi-Square Test. Parametric data compared using Student t-test; p-value <0.05 considered statistically significant.

Table 5 summarizes the logistic regression of factors associated with hyperglycaemia. The significant factors associated with increased risk of hyperglycemia among newly diagnosed PTB patients were history of diabetes (OR = 8.17, p= 0.004), severity of infection (OR = 23.64, p < 0.001) and duration of symptoms (OR= 2.63, p= 0.042).

DISCUSSION

This study investigated the prevalence and determinants of hyperglycemia among newly diagnosed pulmonary tuberculosis patients in the Agona Swedru Municipality. The prevalence of hyperglycaemia was 26%. Additionally, history of diabetes, severity of infection and duration of symptoms were significant determinants of hyperglycemia among our participants. The prevalence rate observed in the current study is similar to a case-control study conducted in Bangalore, South India during 2001–2003 which reported diabetes mellitus as a significant risk factor for developing pulmonary tuberculosis (PTB) (Shetty *et al.*, 2006). The hyperglycemia recorded by Shetty *et al.* (2006) and this study is clearly

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Table 3: Hyperglycemia and diabetes associated characteristics in relation to severity of PTB among newly diagnosed PTB patients

Severity of PTB	Mild (n=54)	Moderate (n=21)	Severe (n=25)	P value
BMI (Kg/m2)	20.28±4.08	21.76 ± 2.30	20.84±2.27	0.235
BMI n (%)				0.853
Underweight	9(16.7)	2 (9.5)	3 (12.0)	
Normal	42(77.8)	17 (81.0)	21 (84.0)	
Overweight	3(5.6)	2 (9.5)	1 (4.0)	
FBG (mmol/L)	5.24±1.14	6.41 ± 1.70*	6.31 ± 0.96*	<0.001
FBG n (%)				<0.001
≤ 6.4	52(96.3)	11 (52.4)	10 (40.0)	
> 6.4	2(3.7)	10 (47.6)	15 (60.0)	
Symptoms of Hyperglycemia				0.249
Headache	29(53.7)	12 (57.1)	16 (64.0)	
Fatigue	12(22.2)	8 (38.1)	15 (60.0)	
History of diabetes				0.057
Yes	3(5.6)	5 (23.8)	2 (8.0)	
No	51(94.4)	16 (76.2)	23 (92.0)	
Polyuria				0.254
Yes	28(51.9)	10 (47.6)	8 (32.0)	
No	26(48.1)	11 (52.4)	17 (68.0)	
Frequency of Polyuria (Daily)				0.551
< 5 times	12(22.2)	6 (28.6)	8 (32.0)	
5-10 times	40(74.1)	15 (71.4)	15 (60.0)	
>10 times	2(3.7)	0 (0.0)	2 (8.0)	
Timing of urination				0.028
Before Cough	29(53.7)	12 (57.1)	6 (24.0)	
After Cough	25(46.3)	9 (42.9)	19 (76.0)	
Polydipsia				0.486
Yes	32(59.3)	12 (57.1)	18 (72.0)	
No	22(40.7)	9 (42.9)	7 (28.0)	
Frequency of Polydipsia (Daily)				0.024
< 5 times	7(13.0)	8 (38.1)	5 (20.0)	
5-10 times	40(74.1)	13 (61.9)	20 (80.0)	
>10 times 7 (13.0)	7(13.0)	0 (0.0)	0 (0.0)	
Timing of Polydipsia				0.043
Before Cough	29(53.7)	13 (61.9)	7 (28.0)	
After Cough	25(46.3)	8 (38.1)	18 (72.0)	

Data presented as frequency (percent). Categorical variable compared using Chi-Square Test. Parametric data compared using Student t-test; p-value <0.05 considered statistically significant.

supported by the study conducted by García-Elorriaga and Del Rey-Pineda (2014) who reported that the association between hyperglycemia and PTB is well documented and there is substantial evidence to support the fact that PTB is an important risk factor for hyperglycemia. Besides, Abate and Chandlia (Abate and Chandalia, 2003) reported that, PTB can induce glucose intolerance and also deteriorate glycemic control in subjects with diabetes mellitus.

Also, a retrospective analysis of 2 years data on tuberculosis subjects from Saudi Arabia in 1998 revealed that 27% had diabetes mellitus related hyperglycemia (Elhadd *et al.*, 2007). Interestingly, Viswanathan *et al.* (2012) also established a pre-diabetes prevalence of 25.3% among PTB patients in a cross–sectional study conducted at

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Table 4: Correlation analyses of severity of PTB with Blood sugar, BMI, Duration of symptoms (months) and Duration after diagnosis of PTB (Weeks)

Parameter		PTB severity	Age	FBG	BMI	DOS	DPTB
PTB severity	R	1	0.06	.490**	0.058	0.505**	0.332**
	P-value		0.554	<0.001	0.566	<0.001	0.001
Age	R		1	0.196	.515**	.219*	0.102
	P-value		.	0.05	<0.001	0.029	0.313
FBG	R			1	.211*	0.123	0.075
	P-value			.	0.035	0.224	0.458
BMI	R				1	0.026	.201*
	P-value				.	0.795	0.045
DOS	R					1	.395**
	P-value					.	<0.001
DPTB	R						1
	P-value						

Spearman's correlation co-efficient analysis

Table 5: Multivariate regression of factors associated with hyperglycemia in newly diagnosed PTB patients

Variable	OR (95% CI)	P-value
Gender		
Male*	Reference	
Female	1.16 (0.45-2.98)	0.759
Age (years)	1.00 (0.98-1.03)	0.735
BMI n (%)		
Underweight	0.68 (0.17-2.65)	0.574
Normal*	Reference	
Overweight	0.50 (0.06-4.48)	0.532
History of diabetes		
Yes	8.17 (1.93-34.50)	**0.004**
No*	Reference	
Severity of PTB		
Mild*	Reference	
Moderate	23.64 (4.53-123.28)	**<0.001**
Severe	39.00 (7.69-197.71)	**<0.001**
Polyuria		
Yes	0.92 (0.38-2.23)	0.849
No*	Reference	
Polydipsia		
Yes	2.73 (0.99-7.56)	0.053
No*	Reference	
Duration of symptoms (months)		
< 5*	Reference	
5-10.	2.63 (1.04-6.69)	**0.042**
>10	0.96 (0.10-9.35)	0.973
Duration after diagnosis of PTB (weeks)		
< 5*	Reference	
5-10.	1.34 (0.41-4.36)	0.626
>10	-	-

https://doi.org/10.51374/annalsmls.2021.1.2.0042

M.V. Hospital for diabetes mellitus in Tamil-Nadu India.

The males had higher prevalence of hyperglycemia and PTB infection compared to the females. Again, duration of symptoms of PTB and hyperglycemia was higher among the males than the females. Also, the males recorded higher values of duration after diagnosis of PTB as compared to their female counterparts. Moreover, it was found out that the frequency of polyuria (within 5 – 10 times daily) was higher in the males than in the females. The findings of this study is apparently supported by a work conducted by Del Prato *et al.* (2007) who recorded a higher prevalence of hyperglycemia among men than women diagnosed with PTB and explained that there might be an accumulative effect of other risk factors such as smoking, and alcohol consumption, which impact PTB (Del Prato *et al.*, 2007).

The mean fasting blood glucose (FBG) also increased significantly with increasing severity of infection. This affirms the assertion made Dooley and Chaisson (2009) that infection of PTB causes insulin resistance and glucose intolerance. It can then be deduced that there is a significant association between the severities of PTB infection and the development of hyperglycemia. A multivariate regression of factors associated with hyperglycemia in newly diagnosed PTB patients revealed that, newly-diagnosed PTB patients with a history of diabetes are 8 times at risk of developing hyperglycemia. This is in consonance with a cross sectional study conducted in Indonesia which reported that diabetes mellitus is a strong risk factor associated with PTB infection (Sen *et al.*, 2009).

An observation from this study showed that PTB patients with moderate (++) and severe (+++) cases of infection were at 24 and 39 times at risk of developing hyperglycemia respectively. This is due to depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon gamma, pulmonary microangiopathy, and micronutrient deficiency and the loss of cell insulin receptor signaling in accordance to the severity of infection (Webb *et al.*, 2009; Ottmani *et al.*, 2010). Our findings cannot be generalized among the PTB population since it was a hospital-based study and not a community-based study. Identifying hyperglycaemia in the PTB population will help in reducing the risk of patients (PTB) patients progressing to diabetes mellitus as diabetes mellitus in PTB contributes to multi-drug resistance. Besides the limited sample size, the single measurement of serum glucose clearly makes it impossible to estimate the proportion of transient hyperglycemia (those that returned to euglycemia state) among the participants. Furthermore, we were unable to establish the association of hyperglycemia with PTB treatment outcomes.

CONCLUSION

The study demonstrated hyperglycemia among newly diagnosed pulmonary tuberculosis patients and the history of diabetes, severity of infection, and the duration of symptoms after diagnosis of tuberculosis before medication were its associated determinants. Fasting blood glucose estimation should be included in the routine management practices of pulmonary tuberculosis patients to ensure proper management of the infection. Further studies should also be conducted on glucose levels among pulmonary tuberculosis patients using higher sample size. This would increase the understanding on the subject.

COMPETING INTEREST

Authors declare that they have no competing interests.

ACKNOWLEDGEMENT

We thank the management of the Swedru Government Hospital for granting us permission to conduct this study. We are also grateful to the following for their support: the staff of the tuberculosis clinic, the laboratory personnel and the tuberculosis patients.

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ISSN 2773-8353