Nexus Between Tuberculosis and Diabetic Mellitus, A Prospective Cohort Study.

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Abstract

Background: This work aimed to describe the clinical presentation of TB in patient with DM, to determine the effects of DM on TB treatment outcomes, to identify the effects of TB on glycemic control, and to describe the lipid profile of TB and DM patients.

Methods: This prospective cohort study design was conducted. The data were collected from September 2018 to June 2020 using patient interviews, examining the patients, chart review, and collecting blood samples. Binary logistic regression was used to identify the determinants of TB treatment outcomes in the context of DM. Kaplan Meier survival curve was used to see the effects of DM on TB clinical response. Linear regression was used to identify the determinants of the HbA1c level during TB infection.

Results: A total of 1092 study participants were included giving for the response rate at 93.81 %. Good TB treatment outcome was observed in 72.5 % of the patients [95 % CI: 69 % - 76 %]. The odds of good TB treatment outcomes were at 75 % lower in the presence of DM (AOR 0.25 [95 % CI: 0.08 – 0.73]). The median time of clinical response in TB and DM patients was 45 days interquartile range (IQR) of 8 days; the median time of clinical response in DM free TB patients was 9 days [IQR 2 days]. TB increased the HbA1c level of DM patients by 1.22 % (B 1.22 [95% CI: 1.11 – 1.34]). In six months period, 60 % of TB and DM patients had got 3 episodes of acute complications.

Conclusion: DM significantly decreases the favorable treatment outcome of DOTS. TB predisposed DM patients for bad glycemic control and increased episodes of acute DM complications.

Background

Diabetes mellitus (DM) is a metabolic disorder characterized by the defects of insulin action, secretion, or a combination of both [1]. DM is classified as type 1 and type 2, the type 2 DM is the most common type reported [2]. World health organization (WHO) estimates that more than 422 million people are living with DM and a total of 1.6 million people died from DM [3]. The situation seriously affecting the low and middle-income countries, in Africa an estimated 19 million people were living with diabetes [4, 5]. In Ethiopia, about 1.7 million people were living with diabetes [6].

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium* species mostly affecting the lung. Each year, TB affects 10 million people and a total of 1.5 million people died from TB [7]. The burden of TB was higher in resource-limited settings. In Ethiopia, the incidence of TB was 151 per 100000 population, and killing 22 individuals per 100000 people [8].

The association between DM and TB is bidirectional. TB increases the risk of DM and DM increases the risk of TB. About 15% of the world's TB cases were attributed by DM [9, 10]. DM decreases cell-mediated immunity, alveolar macrophage, pulmonary microangiopathy, micronutrient deficiency that finally predisposes the patients to acquire TB [11]. TB induces disturbance in the endocrine action of insulin creating a favorable environment to the DM pathogenesis [12]. In the resource-limited settings, there is limited information on the effects of DM on TB and the reverse effects of TB on DM.

Therefore, this study aimed to describe the clinical presentation of TB during DM, to determine the effects of DM on TB treatment outcomes, to identify the effects of TB on glycemic control, and to describe the lipid profile of TB and DM patients.

Methods

A prospective cohort study design was implemented. The study was conducted in the referral hospitals of the Amhara regional state; the region contains 5 referral hospitals namely, Gondar University hospital, Felegehiwote referral hospital, Dessie referral hospital, Debreberhane referral hospital, and Debreworkose referral hospital. The data were collected from September 2018 to June 2020. The data were collected using patient interviews, examining the patients, chart review, and collecting the blood samples. Blood samples were collected and analyzed by trained laboratory technologists. The trained medical doctors participated in data collection. Initially, baseline data were collected from each study participant; then, update data for TB clinical response and adverse drug reaction were collected every week. The episodes of acute DM complications were collected every month. Every six months, we measured the functional status, lipid profiles, and micronutrient levels of the study participants. An International physical activity questionnaire (IPAQ) was used to measure regular physical activity [13]. Medication adherence was measured using the ten-item medication adherence scale (MARS)[14]. High-performance liquid chromatography was used to measure the hemoglobin A one C (HbA1c) level of the patients and its value above 7% indicates bad glycemic control [15]. Problematic alcohol use was screened using the CAGE tool[16]. Good TB treatment outcome was declared if the patient completed the treatments or become smear-negative at the end of DOTS. High-performance liquid chromatography was used to measure the serum vitamin A level of the patient [17], Serum zinc level was measured using atomic absorption spectrophotometer [18, 19], mini Vitek Immune Diagnostic Assay System (VIDAS) machine was used to measure the serum vitamin D level. The functional status questionnaire was used to measure the functional status of the patients [20]. Serum Ferritin was measured using ELISA adhering to the manufacturer's instruction. Lipid profile of the patient was measured using the Cobas Integra 400 Plus clinical chemistry machine (Roche, Switzerland) [21]. Serum albumin was measured using a dye-binding method [22].

The eligibility criteria for this study were DM or TB patients having a regular follow up at the referral hospitals of the region. The study participants unwilling to give consent for the study were excluded. The quality of the study was maintained by conducting a pretest and providing training to the data collectors and supervisors. In addition, the standard operating procedures were adhered to during the laboratory data collection. The sample size was calculated using Epi-info software with the assumption of 95% CI, power of 80%, a risk ratio of 0.8, TB and DM to DM or TB patients ratio of 2, and non-response rate of 10% gives 1164 study participants (388 DM and TB patients, 388 DM free TB patients, and 388 TB free DM patients). The simple random sampling technique was used to select the study participants using their TB or DM registration ID as a sampling frame. Data were entered into the computer using EPI-info software and transferred to the STATA version 14 for the analysis. Descriptive statistics were used to describe the profiles of study participants. Binary logistic regression was used to identify the determinants of TB treatment outcomes in the context of DM. Kaplan Meier survival curve was used to see the effect of DM on TB clinical response. Linear regression was used to identify the determinants of the HbA1c level during TB infection. The paired t-test was used to see the effects of DOTS on lipid and micronutrient levels of the patients. Multiple imputation method was used to handle the missing data.

Ethical clearance was obtained from Bahir Dar University College of Medicine and Health sciences ethical review board (Ethical application number CMHS/IRB/124/2018). A support letter was obtained from Amhara national regional state health bureau and respective hospitals. Written informed consent was obtained from each study participant. Study participants with abnormal laboratory findings were linked to the curative segment.

Results

A total of 1092 study participants were included in the study. The response rate was 93.81%. Twenty-six patients were excluded because of low-quality laboratory samples, 34 study participants were excluded because of their consent, and 12 study participants were excluded because of loss to follow up. The mean age of the study participants was at 32.63 years [SD $\pm$ 15.79 years] with the lowest age of the study subjects at 18 years (Table 1).

Table 1
Profiles of the study participants (n = 1092).

Variables		TB free DM patients(n = 358)		TB and DM patients (n = 361)		DM free TB patients (373)	
		Frequency	%	Frequency	%	Frequency	%
Family size	> 4	194	54.2	350	97	353	94.6
	$\leq$ 4	164	45.8	11	3	20	5.4
Sex	Female	105	29.3	116	32.1	283	75.9
	Male	253	70.7	245	67.9	90	24.1
Regular physical exercise	Present	161	45	94	26	257	68.9
	Absent	197	55	267	74	116	31.1
Residence	Urban	180	50.3	177	49	156	41.8
	Rural	178	49.7	184	51	217	58.2
Problematic alcohol use	Present	53	14.8	203	56.2	92	24.7
	Absent	305	85.2	158	43.8	281	75.3
Marital status	Single	88	24.6	206	57.1	197	52.8
	Married	268	74.9	152	42.1	174	46.8
	Others	2	0.6	3	0.9	2	0.5
Age	$\geq$ 45	53	14.8	75	20.8	76	20.4
	< 45	305	85.2	286	79.2	297	79.6

Tuberculosis in diabetes mellitus patients

A total of 734 TB patients were followed for 6 months; good TB treatment outcome was observed in 72.5% of the patients [95% CI: 69% – 76%]. After adjusting for age, sex, type of TB, DM, family size, problematic alcohol use, physical exercise, HIV, and marital status; TB treatment outcomes were determined by DM, family size, sex, regular physical exercise, HIV, and problematic alcohol use (Table 2).

Table 2
Determinants of TB treatment outcome (n = 734).

Variables		TB prognosis		COR ¹ [95% CI]	AOR ² [95% CI]	P-value
		Good	Bad			
DM	Present	176	185	0.05 [0.03–0.08]	0.25 [0.08–0.73]	0.01
	Absent	356	17			
Sex	Male	211	124	0.41 [0.29–0.58]	1.78 [1.1–2.87]	0.01
	Female	321	78			
Family size	> 4	182	188	0.04 [0.02–0.07]	0.1 9 [0.07–0.59]	< 0.01
	≤ 4	350	14			
Problematic alcohol use	Present	173	122	0.32 [0.23–0.44]	0.55 [0.36–0.84]	< 0.01
	Absent	359	80			
Residence	Urban	252	81	1.34 [0.97–1.87]	1.68 [1.1–2.55]	0.01
	Rural	280	121			
HIV	Positive	93	121	0.14 [0.09–0.2]	0.32 [0.21–0.49]	< 0.01
	Negative	439	81			
Regular physical exercise	Present	302	49	4.09 [2.85–5.9]	1.69 [1.04–2.76]	0.03
	Absent	230	153			

¹COR= crude odds ratio

²AOR=adjusted odds ratio

Interpretation for Table 2

The odds of good TB treatment outcomes were 75% lower in the presence of DM (AOR 0.25 [95% CI: 0.08–0.73]). The odds of good treatment outcome in males were found to be 1.78 folds higher than in the female participants (AOR 1.78 [95% CI: 1.1–2.87]). Higher family size decreased the odds of good treatment outcome by 81% (AOR 0.1 9 [95% CI: 0.07–0.59]). Problematic alcohol use lowered the odds of good treatment outcome by 45% (AOR 0.55 [95% CI: 0.36–0.84]). Good treatment outcomes among urban TB patients were at 1.68 folds higher than rural TB patients (AOR 1.68 [95% CI: 1.1–2.55]). HIV infection lowered the odds of good TB treatment outcomes by 68% (AOR 0.32 [95% CI: 0.21–0.49]).

The clinical profile of TB during DM deviated from the classical TB; the proportion of extra-pulmonary TB was at 75.9% and 55.11% of extra-pulmonary TB was severe, 39.6% of TB presentation was atypical (Table 3).

Table 3
Clinical presentation of TB in DM patients (n = 734)

Variables		DM patients (361)		DM free patients (373)	
		Frequency	%	Frequency	%
Type of TB	Pulmonary	87	24.1	188	50.4
	Extra pulmonary	274	75.9	185	49.6
Severity of extra pulmonary TB	Severe	151	55.11	56	31.11
	Not severe	123	44.89	124	68.89
Atypical TB presentation	Present	143	39.6	15	4
	Absent	218	60.4	358	96
Adverse drug reaction	Present	56	15.5	31	8.3
	Absent	305	84.5	342	91.7
Hepatotoxicity	Present	10	2.77	2	0.54
	Absent	351	97.33	371	99.46

The clinical response of DM and TB patients were significantly delayed as compared to DM free TB patients. The median time of clinical response in TB and DM patients was 45 days interquartile range (IQR) of 8 days; the median time of clinical response in DM free TB patients was 9 days [IQR 2 days].(Fig. 1).

Diabetes mellitus in the context of Tuberculosis

719 DM patients were included. The mean HbA1c level of the patients was at 7.56% [SD $\pm$ 1.12%]. The mean HbA1c level of TB free DM patients was at 6.81% [SD $\pm$ 0.38%]; the mean HbA1c level of DM patients with TB cases was found to be at 8.31% [SD $\pm$ 1.12%].

The glycemic control was good in 40.8% [95% CI: 37.15% – 44.35%] of the patients. Glycemic control was good in 64% [95% CI: 58.97% – 68.96%] of TB free DM patients; the glycemic control was good in 17.7% [95% CI: 13.77% – 21.69%] of DM patients with TB infection. After adjusting for TB, sex, regular physical activity, medication adherence scale, DM duration, DM type, age, Hypertension, HIV, family size, residence; the HbA1c level of DM patient was determined by TB, sex, regular physical activity, medication adherence scale, DM duration, DM type, age, Hypertension (Table 4).

Table 4
The Determinants of HbA1c level in DM patients (n = 719).

Variables	B	t	P-value	95.0% Confidence Interval for B	
				Lower Bound	Upper Bound
TB	1.22	21.65	< 0.01	1.11	1.34
Sex	0.12	2.98	< 0.01	0.04	0.20
Regular physical exercise	-0.12	-2.93	< 0.01	-0.20	-0.04
Medication Adherence Scale	-0.28	-18.46	< 0.01	-0.31	-0.25
DM type	-0.44	-8.93	< 0.01	-0.54	-0.34
Age	0.00	2.45	0.01	0.00	0.01
DM duration	0.06	11.57	< 0.01	0.05	0.07
Hypertension	0.18	3.57	< 0.01	0.08	0.27

Interpretation of Table 4

TB increased the HbA1c level of DM patients by 1.22% (B 1.22 [95% CI: 1.11–1.34]). The HbA1c level of male DM patients was 0.12% higher than female DM patients (B 0.12 [95% CI: 0.04–0.2]). We observed that the regular physical exercise decreased the HbA1c level of DM patients by 0.12% (B -0.12 [95% CI: 0.04–0.2]). Per one unit increase in the medication adherence scale, the HbA1c level of DM patient decreases by -0.28% (B -0.28 [95% CI: 0.25–0.31]). The HbA1c level of type 2 DM patients was 0.44% lower than type 1DM patients (B 0.44 [95% CI: 0.34–0.54]). Per a year increase in the duration of DM, the HbA1c level increases by 0.06% (B 0.06 [95% CI: 0.05–0.07]).

The episodes of acute DM complications have been assessed in this study. Thus, TB patients with DM had frequent episodes of acute complications than with TB free DM patients, 60% of TB and DM patients had 3 episodes of acute complications in 6 months period (Table 5).

Table 5
Episodes of acute diabetic complications in the context of DM (n = 719)

Acute DM complications episodes	TB free DM patients (n = 358)		DM patients with TB infection (n = 361)	
	Frequency	%	Frequency	%
0	304	84.9	25	6.9
1	46	12.8	37	10.2
2	4	1.1	81	22.4
3	4	1.1	217	60.1
4	0	0	1	0.3

DM patients with TB infection have lower baseline micronutrient and lipid profile compared to TB or DM patients; after 6 months the micronutrient level and lipid profile was not increasing to the sufficient level for DM and TB patients (Table 6).

Table 6
Lipid and micronutrient profiles of the study participants (n = 1092)

Profiles	DM patients without TB (n = 358)			TB and DM patients (n = 361)			TB patients without DM (373)		
	Baseline	After 6months	P-value	Baseline	After 6months	P-value	Baseline	After 6month	P-value
Vitamin A in µg/dl ³	37.54	37.09	0.09	27.42	30.06	< 0.01	31.97	38.96	< 0.01
Zinc in µg/dl	93.94	103.99	< 0.01	82.39	88.80	< 0.01	90.87	93.39	< 0.01
Vitamin D in ng/dl ⁴	23.09	26.03	< 0.01	19.78	20.87	< 0.01	20.33	27.80	< 0.01
Ferritin in ng/ml	29.66	30.45	< 0.01	14.88	15.69	< 0.01	18.88	23.32	< 0.01
Albumin in g/dl ⁵	3.52	3.52	0.63	2.88	3.05	< 0.01	3.00	3.37	< 0.01
TCL in mg/dl ⁶	223.43	236.46	< 0.01	200.63	203.85	< 0.01	176.78	187.11	< 0.01
TGL in mg/dl	163.97	145.52	< 0.01	107.22	116.43	< 0.01	108.06	105.29	0.36
HDL in mg/dl	41.69	44.94	< 0.01	34.17	34.67	< 0.01	43.49	49.86	< 0.01
LDL in mg/dl	148.95	162.42	< 0.01	145.02	145.89	0.15	111.69	116.19	< 0.01

³Microgram per deciliter

⁴Nanogram per deciliter

⁵Gram per deciliter

⁶Milligram per deciliter

The baseline functional status of TB and DM patients was poor, after 6 months, the functional status of TB and DM patients did not improve sufficiently (Table 7).

Table 7
Functional status of the study participants (n = 1092)

Parameter	Without TB DM patients(n = 358)				TB and DM patients (n = 361)				TB patients without DM (373)			
	Good		warning zone		Good		warning zone		Good		warning zone	
	Frequency	%	frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Baseline basic activities of daily living	128	35.8	230	64.2	50	13.9	311	86.1	163	43.7	210	56.3
After 6 months basic activities of daily living	126	35.2	232	64.8	92	25.5	269	74.5	328	87.9	45	12.1
Intermediate activity of basic living at baseline	200	55.9	158	44.1	50	13.9	311	86.1	292	78.3	81	21.7
Intermediate activity of basic living after 6 months	201	56.1	157	43.9	221	61.2	140	38.8	352	94.4	21	5.6
Mental health at baseline	256	71.5	102	28.5	81	22.4	280	77.6	317	85	56	15
Mental health after 6 months	257	71.8	101	28.2	215	59.6	146	40.9	358	96	15	4
Work performance at baseline	200	55.9	158	44.1	50	13.9	311	86.1	292	78.3	81	21.7
Work performance after 6 months	198	55.3	160	44.7	175	48.5	186	51.5	349	93.6	24	6.4
Social activities at baseline	200	55.9	158	44.1	50	13.9	311	86.1	292	78.3	81	21.7
Social activities after 6 months	198	55.3	160	44.7	175	48.5	186	51.5	349	93.6	24	6.4
Quality of interaction at baseline	256	71.5	102	28.5	81	22.4	280	77.4	317	85	56	15
Quality of interaction after 6 months	292	81.6	66	18.4	219	60.7	142	39.2	360	96.5	13	3.5

Discussion

In this study we observed good TB treatment outcome at 72.5% of the study patients [95% CI: 69% – 76%], the good TB treatment outcome for DM free TB patients was at 95.4%, only 48.8% of the DM and TB patients have good treatment outcome; The odds of good TB treatment outcome were 75% lower in the presence of DM. This finding agrees with the research conducted in Indonesia [23]. This is due to the high Mycobacterium burden leading to a longer time for culture conversion[24]. Additionally, DM affects the pharmacokinetics of anti-TB drugs by reducing their plasma concentration [25].

The proportion of pulmonary TB was lower in the presence of DM, only 24.1% of the TB cases were pulmonary and 55.11% of them were extra-pulmonary TB which was found to be very severe. This finding was in-line with the findings in Georgia [26]. This is due to the effects of DM on the

smear production and excretion that affects the detection of TB, indicating that a significant number of pulmonary TB was not detected in DM patients [27].

Atypical TB was common in DM patients reaching 40% of the TB patients. This finding is consistent with the findings in Brazil [28]. This indicates that the TB diagnostic algorithm should be revised in the case of DM as reported with the study in India [29].

In this study, 15.5% of the DM patients manifested with adverse TB reaction compared to 8.3% of the adverse drug reaction in TB patients without DM. The reason might be due to the high pills burden of TB-DM patients that finally predisposed the patients for the adverse drug reactions [30].

In this study, the median time of clinical response in TB and DM patients was 45 days, interquartile range (IQR) of 8 days; the median time of clinical response in DM free TB patients was 9 days [IQR 2 days]. This is consistent with the previous report in Ethiopia [31], suggesting that the treatment algorithm should be revised in TB-DM patients in Ethiopia.

In our study, we observed that TB increased the HbA1c level of DM patients by 1.22%. The mean HbA1c level of the patients was at 7.56% [SD $\pm$ 1.12%]. The mean HbA1c level of TB free DM patient was 6.81% [SD $\pm$ 0.38%]; the mean HbA1c level of DM patients with TB was 8.31% [SD $\pm$ 1.12%]. The glycemic control was good in 40.8% [95% CI: 37.15% – 44.35%] of the patients. Glycemic control was good in 64% [95% CI: 58.97% – 68.96%] of TB free DM patients; the glycemic control was good in 17.7% [95% CI: 13.77% – 21.69%] of DM patients with TB infection. This finding agrees with the findings in India [32]. This is due to the reason that TB induces glucose intolerance worsening the glycemic control of DM patients [33].

In our study, we observed that excess episode of acute DM complications in DM and TB patients; in the 6 months period, 60% of the TB and DM patients which had found to be 3 episodes of acute complications compared to 15% of cumulative complications in TB free DM patients. This finding is comparable with the finding in Mexico [34]. This is be due to the effects of infection on inducing the stress hormones that disturbs insulin metabolism [35, 36].

After DOTS completion, Vitamin A increased by 2.65 $\mu\text{g}/\text{dl}$ for DM and TB patients, as compared to 7 $\mu\text{g}/\text{dl}$ increment for DM free TB patients. This strengthens the justification that, higher complications rate of DM among TB patients was attributed to low vitamin A level.

The baseline serum zinc level of DM and TB patients was 88.23 $\mu\text{g}/\text{dl}$, while the baseline serum zinc level of DM free TB patients was 90.87 $\mu\text{g}/\text{dl}$. This finding agrees with findings from India [37]. This will strengthen the necessity of zinc supplementation for DM patients [38].

In this study, vitamin D increased by 1.1 ng/dl for DM and TB patients, and its values increased by 7.46 ng/dl for DM free TB patients. This finding agrees with the finding in Korea [39]. This finding implies that the critical role of vitamin D was limited in TB-DM patients.

The study indicated that the baseline Ferritin level of DM and TB patients was 14.88 ng/ml whereas the baseline Ferritin level of DM free TB patients was 18.88 ng/ml. The finding was consistent with previously available literature regarding the association between DM and Ferritin. This is due to the high burden of anemia in our study areas [40].

In our study we observed that the HDL level of DM and TB patients was at 34.17 mg/dl, the baseline HDL level of DM free TB patients was at 43.49 mg/dl. The finding was in line with the finding in Netherland [41], suggesting high malnutrition burdens in the study area [42].

In DM and TB group, the basic activity of daily living was improved by 11.6% for the good zone, 44.5% increment for the good zone was observed in DM free TB patients. This finding is in agreement with the findings in Netherland [43]. This urgently calls great attention of decision-makers to revise the management of the two morbidities during co-existence.

The main limitation of this research work was a failure to identify the effects of TB on the chronic complications of DM and the effect of DM on the relapse of TB.

Conclusion

In the studied region, we observed DM significantly decreased the favorable treatment outcome of DOTS. DM makes the TB presentation atypical and delays the clinical response and disturbs the lipid and micronutrient profiles of TB patients. TB predisposes the DM patients for bad glycemic control and increased the episodes of acute DM complications. Furthermore, TB decreased the functional status of DM patients.

Abbreviations

- $\mu\text{g}/\text{dl}$: Microgram per deciliter
- AOR: Adjusted odds ratio
- B: Beta coefficient

- CI: confidence interval
- COR : Crude odds ratio
- DM: Diabetes mellitus
- DOTS: Directly observed treatment strategy
- ELISA: Enzyme linked immune sorbent assay
- g/dl: Gram per deciliter
- HbA1c: Hemoglobin A one c
- HIV: Human immune deficiency virus
- IPAQ: International physical activity questionnaire
- IQR: Interquartile range
- MARS: Medication adherence scale
- mg/dl: Milligram per deciliter
- ng/dl: Nanogram per deciliter
- SD: Standard deviation
- TB: Tuberculosis
- WHO: World health organization

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from Bahir Dar University College of Medicine and Health sciences ethical review board (Ethical application number CMHS/IRB/124/2018). A support letter was obtained from Amhara national regional state health bureau and respective hospitals. Written informed consent was obtained from each study participant. Study participants with abnormal laboratory findings were linked to the curative segment.

Consent for publication

Not applicable

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declares that they have no competing interests

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Author contribution

BEF and TEF conceived the experiment; BEF, MBK, WKA, MBK, WKA, AS, SH, TT, FB and TEF performed the experiment, plan the data collection process, analyzed and interpreted the data. BEF, MBK, WKA, MBK, WKA, AS, SH, TT, FB and TEF wrote the manuscript and approved the final draft for publication.

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Questionnaire

The questionnaire of the study were taken from the following references

- Sjostrom M, Ainsworth B, Bauman A, Bull F, Hamilton-Craig C, Sallis J: **Guidelines for data processing analysis of the International Physical Activity Questionnaire (IPAQ)-Short and long forms.** 2005.
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Figures

Figure 1

The median time of clinical response in DM free TB patients was 9 days [IQR 2 days]

Supplementary Files

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- [STROBEchecklistcohort.docx](#)