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Cohort profile of the diabetes-tuberculosis treatment outcome (DITTO) study in Pakistan

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Abstract

Purpose: Pakistan is faced with an increasing prevalence of diabetes in addition to its existing high burden of tuberculosis. Diabetes has a detrimental effect on treatment outcomes of tuberculosis patients, which may hinder the achievement of End-TB strategy by 2030. We conducted a prospective cohort study to generate contextual and valid scientific evidence to determine difference between treatment outcomes among diabetic and non-diabetic tuberculosis patients from a developing country like ours with its unique interplay of socio- cultural, economic and health system factors, to inform policy and practice.

Participants: This paper outlines the study and baseline characteristics of 614 new cases of pulmonary tuberculosis (PTB) aged 15 years and older, which were followed up prospectively while on anti-tuberculosis treatment and after treatment completion.

Findings to date: We ascertained patients' diabetic status by conducting random and fasting blood glucose tests and their glycemic control by determining glycosylated hemoglobin. Treatment outcomes are established using standardized definitions provided by World Health Organization. Anthropometric measurements helped establish body mass index of patients. The assessment of 614 respondents' diabetic status revealed that 113 (18%) were diabetic and 501 (82%) were non-diabetic. A significantly greater proportion of diabetic PTB patients as compared to non-diabetic PTB patients were illiterate (65%), married (89%), gave history of heart disease (88%) and hypertension (67%) and were overweight (67%) and obese (53%). Unfavourable treatment outcome was more likely among diabetic PTB patients as opposed to non-diabetic PTB patients.

Future plans: We are negotiating with the government regarding funding for further follow up of the cohort to ascertain death and relapse; and differentiate between re-infection and recurrence among these patients with respect to their diabetic status. This will provide new insights into co-management of the two diseases.

Strengths and Limitations of this study

- The diabetes tuberculosis treatment outcome (DITTO) study is the first prospective cohort study, which has been conducted in Pakistan to determine the effect of diabetes on treatment outcome of TB patients.
- The exposure status of DITTO cohort was based upon two tests; one random and the other fasting blood glucose test.
- The main limitation is the inability to conduct drug susceptibility testing of patients at the time of recruitment into the DITTO cohort.
- The HIV status of PTB patients was not determined.

Introduction

There is a resurgence of interest in the dual epidemic of diabetes and tuberculosis with the global increase in the diabetic population. This converging epidemic of diabetes and tuberculosis has many untoward and detrimental effects.[1] The risk of development of tuberculosis is tripled by diabetes.[2] It increases the mortality and severity related to tuberculosis and also slows the response to tuberculosis treatment.[3] The clearance of tuberculosis mycobacterium from the sputum, which is required to declare the patient non infectious is also delayed by diabetes.[4] Diabetes increases the risk of treatment failure, death and relapse among patients with tuberculosis, which poses a challenge for both the developed and the developing world.[1,5]

Developing countries like Pakistan are likely to be affected the most as they are struggling with their existing high burden of tuberculosis and in addition have to tackle with the growing population of diabetics. Pakistan ranks 4th in terms of global burden of TB with an estimated incidence of 231 cases per 100,000 population.[6] Pakistan is one of the 10 countries with the highest number of diabetes patients and a prevalence ranging from 7.6% to 11%.[7,8] It is feared that diabetes mellitus co-morbidity will hinder the achievement of the long-term rates of eliminating tuberculosis. Tuberculosis will be considered eliminated if by year 2050 there is less than one incident case of the disease per one million population.[3, 9]

Most of the scientific knowledge regarding association between diabetes and tuberculosis has been generated in industrialized countries.[10] In addition, the published literature suffers from certain limitations. The majority of studies are either cross-sectional, case control or retrospective cohort studies, the ascertainment of patient's diabetic status is based on past records, and a substantial number of studies fail to control for important confounders.[11] Furthermore, good quality evidence needs to be generated from developing countries which can help in addressing this problem. Pakistan has a high burden of tuberculosis and a rapidly growing population of diabetics. Data is scarce regarding the impact of diabetes on tuberculosis treatment outcome in Pakistan. Therefore this prospective cohort study was undertaken to determine the difference between treatment outcomes in diabetic and non-diabetic patients of pulmonary tuberculosis and identify the determinants of treatment outcomes in patients of pulmonary tuberculosis with and without diabetes mellitus

Cohort Description

The recruitment and enrollment of new adult cases of pulmonary TB (PTB) that were diagnosed, registered and received complete treatment at Gulab Devi Chest Hospital (GDH), Lahore began in October 2013. A new case was a PTB patient, both sputum smear positive and sputum smear negative who had never taken TB drugs in the past, or had taken TB drugs for less than 4 weeks in the past but was not registered with National Tuberculosis Control Program (NTP). An adult was a PTB patient aged 15 years or older.[12] Patients with previous history of anti-tuberculosis treatment (ATT), who were not sure or were unable to recall previous therapy with ATT and who were severely ill, disabled or mentally ill were excluded from participation in the study. All eligible PTB patients willing to participate after giving informed written consent were enrolled in the study cohort.

The enrolment period lasted upto March 2014, till the sample size of 614 participants was successfully achieved. The enrolled PTB patients' exposure status was ascertained, by conducting random blood glucose (RBG) and fasting blood glucose (FBG) tests. The diabetic PTB and the non-diabetic PTB patients were followed up prospectively, while on standardized Category I treatment consisting of fixed dose combinations for adults in accordance with current guidelines of NTP.[13] The intensive phase of treatment was of two months, in which Rifampicin, Isoniazid, Ethambutol and Pyrazinamide was given to all the patients on a daily basis. This was followed by a continuation phase of four months in which a daily dose of Isoniazid and Rifampicin was given to all patients.

Follow Up

The two groups comprising of exposed (diabetic) PTB patients and unexposed (non-diabetic) patients were followed up prospectively at 2nd, 5th and 6th months of ATT treatment and also at 6 months after treatment completion as shown in figure 1 below. The follow up schedule was thoroughly explained to respondents at recruitment and follow-up visits were scheduled to coincide with patients' drug collection time from GDH. At the time of recruitment, patients' contact details were gathered which included home addresses and two telephone numbers (landline or mobile) belonging either to them, a family member or neighbor to facilitate the follow up process. Follow up reminders were sent through telephone calls. The contact information of the respondents was reviewed at each subsequent visit to aid in efficient follow up. The follow up period was from December 2013 to March 2015.

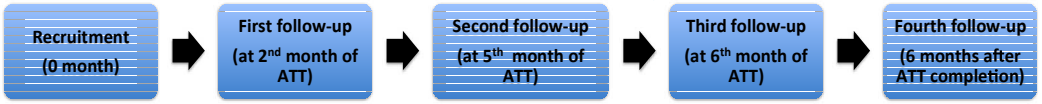
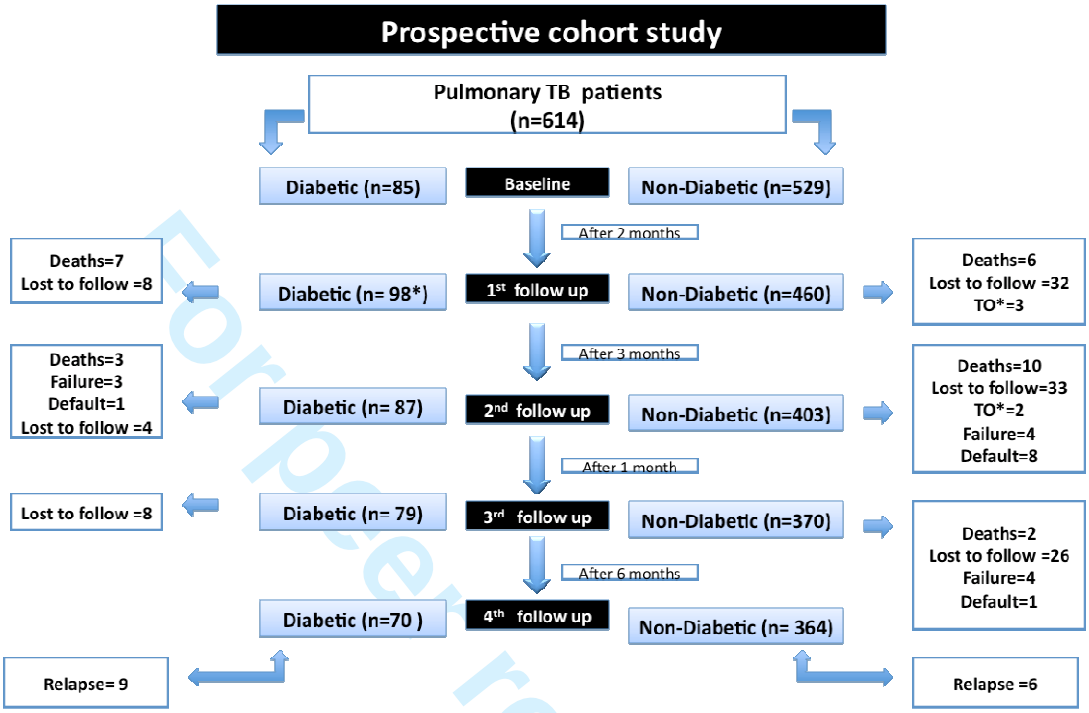


Figure 1: Follow up schedule of PTB patients on ATT at Gulab Devi Hospital, Lahore

The first follow up was scheduled at two months after recruitment. The follow up completion rate at this first follow up was 93.4%, with 40 participants lost to follow up. The total number of participants entering the second follow up comprised of 558 PTB patients instead of 574, as 16 participants experienced a treatment outcome, which included 13 deaths and 3 transferred out patients. The follow up completion rate for the second phase was 93.3%, with 37 PTB patients lost to follow up. For the third phase, the completion rate was 93% and 34 patients were lost to follow up. The follow-up completion rate of the fourth phase was 100%; however, the overall follow up completion rate of the 614 PTB patients was 81.9%, with 111 patients lost to follow up. The figure 2 that follows highlights the number of respondents lost to

follow up at each phase of the study and also the number who experienced a treatment outcome during and at the end of ATT and also after treatment completion.



* Known diabetics + newly diagnosed diabetics

Figure 2: Flow diagram depicting the follow up periods of the PTB cohort along with treatment outcome and loss to follow up at Gulab Devi Chest Hospital, Lahore

The common reasons for lost to follow up included; patients movement to another city, patients in denial of their disease status, patients attributing their signs and symptoms to black magic / super-natural power, patients claiming they were incorrectly diagnosed and the inability to contact the patient through telephone calls and home visits.

Additional data

Interview

Trained male and female data collectors conducted the interviews. Both were employed as full-time data collectors who worked six days a week in the OPD of GDH. Data were collected on structured questionnaires from the study participants at the time of recruitment and at each follow up visit. The variables studied included socio-demographic characteristics such as age, gender, education, occupation,

income, area of residence and marital status. Lifestyle and behavioural characteristics, which included smoking status, alcohol consumption status, history of imprisonment, body mass index (BMI) and drug abuse were also determined. Patients clinical presentation variables included cough longer than 3 weeks, prolonged fever, difficulty in breathing, presence of blood in sputum, night sweats, weight loss and type of PTB. Also history of co-morbidities such as hypertension, heart disease, renal disease and asthma was inquired. Other variables studied include type of diabetes, glyceamic control among the diabetics, family history of diabetes, exposure to a household TB contact and adherence to DOTS therapy or not.

Measurement of height and weight

The height of the PTB patients was measured with a stadiometer to the last complete 0.1cm and rounded to the nearest whole number while patients were standing erect without shoes. The weight of these patients was measured on a standing scale with minimal clothing on to the last 0.1kg and rounded to the nearest whole number. Throughout the study the same instruments were used which were calibrated every day to ensure validity of the results.[14]

Estimation of blood sugar

The patients' diabetic status was ascertained by performing two tests on those PTB patients who were unaware of their diabetic status. These tests included a RBG test conducted at baseline and a FBG test conducted at first follow up visit, which coincided with second month of ATT treatment. (Figure 3)

Random blood glucose test

Patients' RBG was estimated using the Accu-Check® Active glucometer by Roche®. A lancing device was used to prick the fingertip of the patient. The fingertip was gently squeezed and a small drop of blood was placed on the square orange mark on the test strip inserted in the glucometer until an hourglass appeared and the result was displayed on the display. It was ensured that the number on the display matched the code number on test strips container as a quality control measure. A sterile swab was used to clean the finger. All patients having a RBG $\geq$ 110mg/dl were offered FBG testing.

Fasting blood glucose test

Patients were explained to fast overnight i.e 8 hours before coming for their first follow up visit at the second month of ATT. They were reminded of the fast through telephone calls twice before their arrival at the health facility; once a week before their date of visit to the hospital and second call a day before the visit so as to ensure their eligibility for the FBG test. For the FBG estimation the same procedure as mentioned above was carried out. However, before conducting the test patients were again inquired regarding their overnight fast confirming their fasting status. And in case of any suspicion of food intake, the patient was asked to come the next day for FBG test. Patients having a FBG $\geq$ 126mg/dl were diagnosed as diabetic. The diabetics were referred to a specialist for management of their newly diagnosed disease. [15,16]

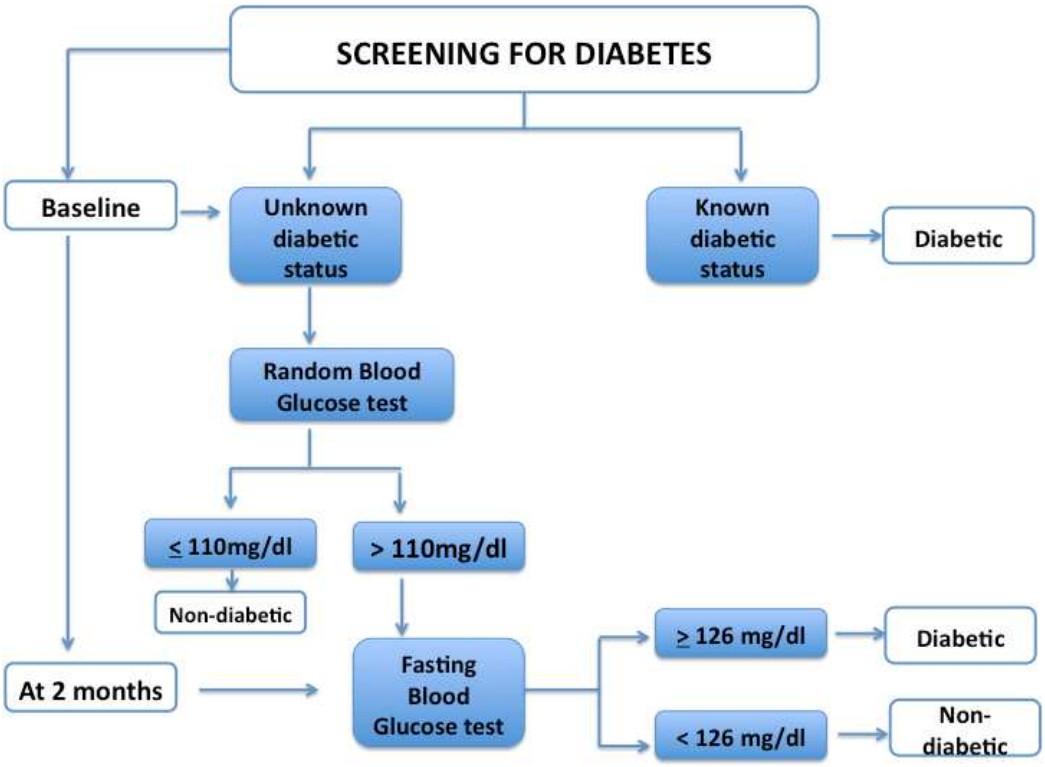


Figure 3: The protocol used in screening PTB patients for diabetes

Sputum smear examination

The diagnosis of PTB patients and assessment of treatment outcomes was established by performing sputum smear microscopy using Ziehl-Nelson (ZN) staining technique by the laboratory staff of GDH under the NTP. Presence of acid-fast bacillus (AFB) was checked in the sputum sample after preparing a sputum smear on a glass slide followed by its staining and fixation. The reporting of AFB was done as is depicted in table 1 below:

Table 1: Reporting AFB through sputum smear microscopy[12]

Seen on slide	Result	Positive (grading)	Bacterial Load
More than 10AFB per field	POS	3+	Heavy
1-10AFB per field	POS	2+	Medium
10-99AFB per field	POS	1+	Low
1-9 AFB per field	POS	Scanty	Very low
No AFB per field	NEG		Nil/ Not seen

The results' of the sputum sample were communicated by the laboratory personnel to OPD staff, who recorded it on the patients' treatment card and in hospitals TB registers for record. The results were acquired by the data collectors of the study from the patient treatment card and verified with the hospital TB registers.

Estimation of glycosylated haemoglobin

At the second follow up visit which coincided with the 5th month of ATT, a blood sample was drawn from all known and the newly diagnosed diabetic PTB patients for the estimation of gylcosylated hemoglobin and hence assessment of their glycaemic control. A 3c.c. sample of blood was obtained through venipuncture by the data collectors using a disposable syringe and using aseptic technique. The blood was immediately transferred to an ethylene di-amine tetra acetic acid (EDTA) tube, which was gently inverted to ensure mixing of the components. The specimen was transported on a daily basis to the pathology laboratory of Punjab Institute of Cardiology (PIC), where they were analyzed for hemoglobin A1c (HbA1c) using high performance liquid chromatography (HPLC). A HbA1c value of $\leq$ 7% was considered as normal value and a HbA1c value >7% was considered as an abnormal value in the study.[17]

Treatment Outcomes

All the patients were followed up to determine treatment outcomes. The standardized treatment outcome definitions given by the NTP, Pakistan and the WHO were used in the study.[18,19] The treatment outcomes included:

Cured: A sputum smear positive patient, who had completed 6 months of treatment and became sputum smear negative at the end of treatment and on at least one previous occasion.

Treatment completed: A sputum smear positive patient, who completed 6 months of treatment and had at least one follow up smear negative result and none at the end of treatment due to any reason or smear negative cases who completed six months of treatment successfully.

Death: A patient who died for any reason during the course of treatment.

Failure: A sputum smear positive patient who remained positive or again became positive at 5 months or a sputum smear negative patient found to be smear positive at the end of 2 months.

Default: A patient whose treatment was interrupted for two consecutive months or more after registration. (According to new definition this treatment outcome is called "Loss to follow up")

Transferred out: A patient who was transferred to another centre and for whom the treatment outcome was not known. (According to new definition this treatment outcome is called "Not Evaluated")

Relapse: A patient who was previously treated for TB, was declared cured or treatment completed at the end of their treatment and was diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).[19]

The figure 4 below depicts the various data collection activities undertaken by the DITTO study.

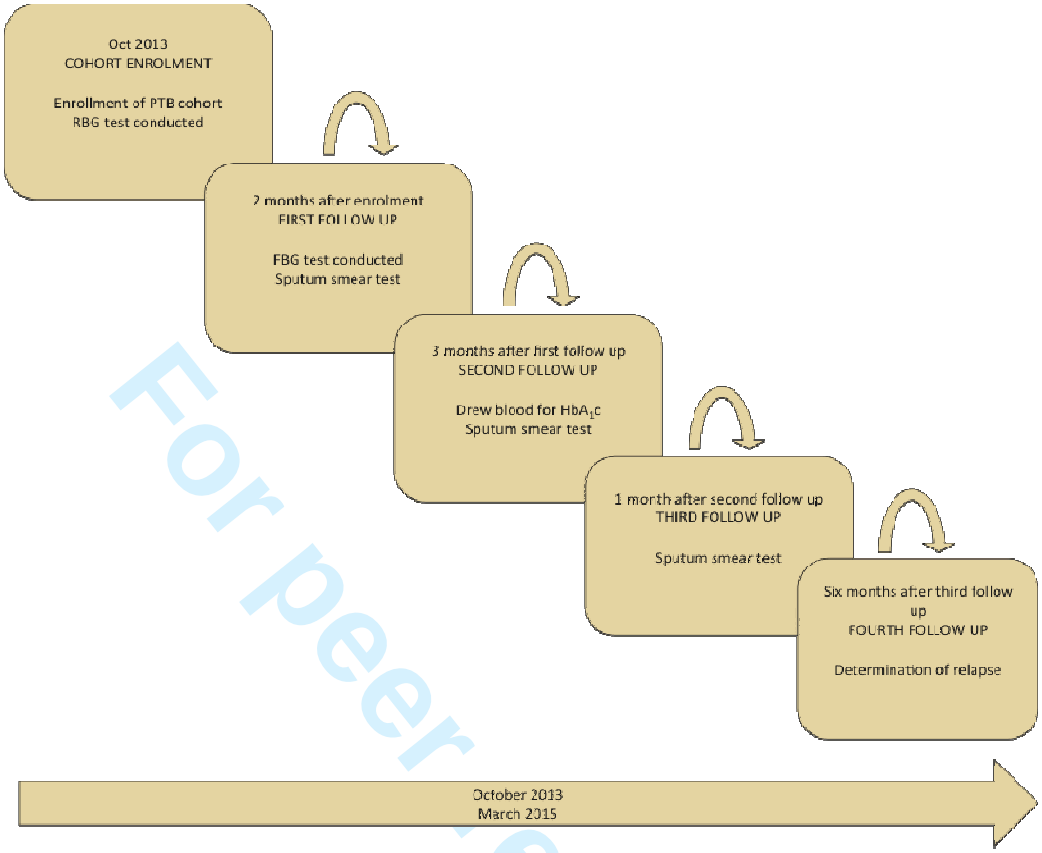


Figure 4: Flow diagram of data collection activity at Gulab Devi Hospital, Lahore

Characteristics of the study population

The assessment of 614 respondents' diabetic status revealed that 113 (18%) were diabetic and 501 (82%) were non-diabetic. The age distribution of the PTB cohort comprising 113 (18%) diabetics and 501 (82%) non-diabetics shows the diabetic PTB respondents' to be older as compared to the non-diabetic PTB respondents'. The age category of 50 years and above incorporated 58 (51%) diabetic PTB patients versus 55 (11%) non-diabetic PTB patients. The youngest age category of 15-19 years had majority of non-diabetics (n=134,27%) as compared to diabetics (n=1,1%) (p=0000). A greater proportion of diabetic PTB patients were illiterate (n=74,65%) than the non-diabetic PTB patients (n=249,50%). (p=0.035) and most PTB diabetics were married (n=101,89%) as opposed to non-diabetics (n=243,48%) (p=0000). The majority of the exposed PTB patients were overweight (n=18,67%) and obese (n=9 ,53%), whereas, majority of un-exposed respondents were underweight (n=289,94%). (p=0.000) More diabetics as compared to non-diabetics gave history of heart disease (n=14,88%) and hypertension (n=26,67%). (p=0.000) as is depicted in table 2 below.

Table 2: Profile of 614 new pulmonary tuberculosis patients with (n=113) or without diabetes mellitus (n= 501) presenting at Gulab Devi Chest Hospital, Lahore

	PTB with Diabetes n=113		PTB without Diabetes n=501		Total n=614	P-value
	n	%	n	%	n (%)	
Age Group (in years)						0.000
15-19	1	1	134	99	135 (22)	
20-24	4	3	138	97	142 (23)	
25-29	4	6	63	94	67 (11)	
30-39	16	18	74	82	90 (15)	
40-49	30	45	37	55	67 (11)	
>50	58	51	55	49	113 (18)	
Gender						0.357
Male	53	17	259	83	312 (51)	
Female	60	20	242	80	302 (49)	
Residence						0.179
Urban	84	20	340	80	424 (69)	
Rural	29	15	161	85	190 (31)	
Educational qualification						0.035
Illiterate	74	23	249	77	323 (52)	
Primary	13	15	71	85	84 (14)	
Matriculation	20	14	126	86	146 (24)	
Intermediate	5	17	25	83	30 (5)	
Bachelors	1	6	17	94	18 (3)	
Masters and above	0	0	13	100	13 (2)	
Income Category (Rupees)						0.113
Nil[‡]	73	19	311	81	384 (63)	
<5000	5	12	38	88	43 (7)	
5100-8000	6	9	61	91	67 (11)	
8100-11000	10	18	44	82	54 (9)	
11100-14000	7	27	19	73	26 (4)	
14100-17000	6	29	15	71	21 (3)	
>17100	6	32	13	68	19 (3)	
Marital status						0.000
Married	101	29	243	71	344 (56)	
Single	12	4	255	96	267 (43.5)	
Divorced	0	0	1	100	1 (0.2)	
Widowed	0	0	2	100	2 (0.3)	
BMI[*]						0.000
Less than 18.50	18	6	289	94	307 (51)	
18.50 – 24.99	63	24	194	76	257 (42)	
25 – 29.99	18	67	9	33	27 (4)	
30 and above	9	53	8	47	17 (3)	
Heart disease						0.000

Yes	14	88	2	12	16 (3)	
No	99	17	499	83	598 (97)	
Hypertension						0.000
Yes	26	67	13	33	39 (6)	
No	87	15	488	85	575 (94)	

‡Income in the form of loans/ help from relatives/extended family/friends
* Body mass index, of 608 patients

Findings to date

The treatment outcome analyzed as a binary variable shows 69 (14%) patients had an unfavourable outcome and 434 (86%) had a favourable outcome. In univariate analysis, patients with diabetes were more likely to experience an unfavourable outcome than patients without diabetes (OR=2.6, 95% CI: 1.48 to 4.56,p = 0.001). Other studies conducted in Taiwan and South Korea have also reported an increased risk of unfavourable treatment outcome among diabetic PTB patients as compared to non-diabetic PTB patients i.e an OR of 1.46 (95% CI of 1.03 to 2.08)[20] and 1.78 (95% CI= 1.07 to 2.95)[21] respectively.

Strengths and weaknesses

The strengths of our study included employing a rigorous study design i.e the prospective cohort study design, which generates valid results as opposed to other observational epidemiological study designs in our endeavour to determine treatment outcomes among tuberculosis diabetic patients. The data collection tool gathered information on all possible confounders identified through literature review and having biological plausibility. These confounders were thus adjusted for in the analysis producing valid results. The exposure status of PTB patients' was based upon two tests; one random and the other fasting blood glucose test. The confirmatory FBG test was conducted two months after initiation of ATT to rule out the bias associated with transient stress induced hyperglycemia attributed to tuberculosis disease. Lastly, standardized treatment outcome definitions provided by WHO were used in the study. To our knowledge, no previous study has been conducted in Pakistan to determine the effect of diabetes on treatment outcome of TB patients.

The study found it beneficial to employ both a male and a female data collector who were trained for gender matched data collection considering the prevailing cultural environment. We ensured negligible data collector turnover, which helped develop a good rapport between the researcher and respondents. Additionally, we provided a 24 hour helpline, which was very popular among the patients, was greatly appreciated by them and helped develop sustained relationships with them; maximizing response rate.

However, there were certain limitations in our study. The drug susceptibility testing was not done among the PTB cohort at the time of enrollment or during the course of ATT, which could have led to bias in the results. However because of our inclusion criteria of recruiting only the new PTB patients, with no prior history of ATT intake drug resistance may not be an issue. The difference in drug resistance patterns

between the two groups was unlikely to have contributed to the observed results. Secondly, HIV status, which has been identified as a strong risk factor for adverse treatment outcome among TB patients, was not determined. Lastly, we were unable to study the effect of glucose control on TB treatment outcome as HbA1c values for the entire cohort were not available. Due to resource constraints glycosylated hemoglobin blood analyses was performed of only the diabetics in the study. If treatment outcome among diabetic PTB patients is modified by glucose control, our results could be affected. However, according to Mi F et al, 2 month and 6 month FBG levels among PTB patients did not have statistically significant association with adverse outcomes.[22]

Collaboration

The data is not available freely, however we welcome specific and detailed proposals for collaboration. Enquiries and requests for further information should be made to fatimamukhtar@doctor.com

Authors' Contributions: FM contributed to conception and design of the work, acquisition, analysis and interpretation of data and write up. ZAB contributed to conception of work, analysis of data, revised the work for intellectual content and approved the final version to be published.

Competing interests: None declared.

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Abstract

Purpose: Pakistan is faced with an increasing prevalence of diabetes in addition to its existing high burden of tuberculosis. Diabetes has a detrimental effect on treatment outcomes of tuberculosis patients, which may hinder in achieving the goals of the End-TB strategy by 2030. We conducted a prospective cohort study to determine difference between treatment outcomes among diabetic and non-diabetic new pulmonary tuberculosis patients. This would help generate contextual and valid scientific evidence from a developing country like ours with its unique interplay of socio- cultural, economic and health system factors, to inform policy and practice.

Participants: This paper outlines the baseline characteristics of 614 new cases of pulmonary tuberculosis (PTB) aged 15 years and older, which were followed up prospectively at the 2nd, 5th and 6th month while on anti-tuberculosis treatment and 6 months after treatment completion.

Findings to date: We ascertained patients' diabetic status by conducting random and fasting blood glucose tests and their glycemic control by determining glycosylated hemoglobin. Treatment outcomes were established using standardized definitions provided by World Health Organization. The assessment of 614 respondents' diabetic status revealed that 113 (18%) were diabetic and 501 (82%) were non-diabetic. A greater proportion of diabetic PTB patients were illiterate (n=74/113,65.5%) as compared to non-diabetic PTB patients (n=249/501,50%) (p=0.035). More PTB diabetic patients gave history of heart disease (n=14/113,12%) and hypertension (n=26/113, 23%) as compared to non-diabetic PTB patients (n=2/501,0.4%) and (n=13,501,3%) (p<0.001) respectively. Unfavourable treatment outcome was more likely among diabetic PTB patients (n=23/93,25%) as opposed to non-diabetic PTB patients (n=46/410,11%)(p=0.001).

Future plans: We are negotiating with the government regarding funding for a further two year follow up of the cohort to ascertain death and relapse in the post treatment period; and also differentiate between re-infection and recurrence among these patients with respect to their diabetic status.

Strengths and Limitations of this study

- The diabetes tuberculosis treatment outcome (DITTO) study is the first prospective cohort study, which has been conducted in Pakistan to determine the effect of diabetes on treatment outcome of TB patients.
- The ascertainment of diabetic status of DITTO cohort was based upon two tests; one random and the other fasting blood glucose test.
- The main limitations are the inability to conduct drug susceptibility testing of patients and to determine their HIV status at the time of recruitment into the DITTO cohort due to non-availability of funds.

Introduction

There is a resurgence of interest in the dual epidemic of diabetes and tuberculosis with the global increase in the diabetic population. This converging epidemic of diabetes and tuberculosis has many untoward and detrimental effects.[1] The risk of development of tuberculosis is tripled by diabetes.[2] It increases the severity related to tuberculosis and also slows the response to tuberculosis treatment.[3] The clearance of tuberculosis mycobacterium from the sputum, which is required to declare the patient non infectious is also delayed by diabetes.[4] Diabetes increases the risk of treatment failure, death and relapse among patients with tuberculosis, which poses a challenge for both the developed and the developing world.[1,5]

Low and middle income countries like Pakistan are likely to be affected the most as they are struggling with their existing high burden of tuberculosis and in addition have to tackle with the growing population of diabetics. Pakistan ranks 4th in terms of global burden of TB with 630,000 cases and an estimated incidence of 231 cases per 100,000 population.[6,7] Pakistan is one of the 10 countries with the highest number of diabetes patients and a prevalence ranging from 7.6% to 11%.[8,9] It is feared that diabetes mellitus co-morbidity will hinder the achievement of the long-term rates of eliminating tuberculosis. Tuberculosis will be considered eliminated if by year 2050 there is less than one incident case of the disease per one million population.[3,10]

Most of the scientific knowledge regarding association between diabetes and tuberculosis has been generated in industrialized countries.[11] And recently China and India have made valuable contributions.[12,13] But, the published literature suffers from certain limitations. The majority of studies are either cross-sectional, case control or retrospective cohort studies, the ascertainment of patient's diabetic status is based on past records, and a substantial number of studies fail to control for important confounders.[5,14,15] Furthermore, good quality evidence needs to be generated from developing countries which can help in addressing this problem. Pakistan has a high burden of tuberculosis and a rapidly growing population of diabetics. Data is scarce regarding the impact of diabetes on tuberculosis treatment outcome in Pakistan. Therefore this prospective cohort study was undertaken to determine the difference between treatment outcomes in diabetic and non-diabetic patients of pulmonary tuberculosis and identify the determinants of treatment outcomes in patients of pulmonary tuberculosis with and without diabetes mellitus.

Cohort Description

The recruitment and enrollment of new adult cases of pulmonary TB (PTB) that were diagnosed, registered and received complete treatment at Gulab Devi Chest Hospital (GDH), Lahore began in October 2013. The diagnosis of PTB, both sputum smear positive and sputum smear negative was made according to the definition given by the National Tuberculosis Control Program (NTP).[16] A new case was a PTB patient, both sputum smear positive and sputum smear negative who had never taken TB drugs in the past, or had taken TB drugs for less than 4 weeks in the past but was not registered with National Tuberculosis Control Program (NTP). An adult was a PTB patient aged 15 years or older.[16] Patients with previous history of anti-tuberculosis treatment (ATT), who were not sure or were unable to recall previous therapy with ATT and who were severely ill, disabled or mentally ill were excluded from participation in the

study. All eligible PTB patients willing to participate after giving informed written consent were enrolled in the study cohort.

The enrolment period lasted upto March 2014, till our sample size of 614 participants was successfully achieved. We recruited 614 PTB patients based on our statistical calculations for cohort studies using WHO software for sample size calculation in health studies.[17] The enrolled PTB patients' diabetic status was ascertained. The diabetic PTB and the non-diabetic PTB patients were followed up prospectively, while on standardized Category I treatment consisting of fixed dose combinations for adults in accordance with current guidelines of NTP.[18] The intensive phase of treatment was of two months, in which Rifampicin, Isoniazid, Ethambutol and Pyrazinamide was given to all the patients on a daily basis. This was followed by a continuation phase of four months in which a daily dose of Isoniazid and Rifampicin was given to all patients.

Follow Up

The two groups comprising of exposed (diabetic) PTB patients and unexposed (non-diabetic) patients were followed up prospectively at 2nd, 5th and 6th months of ATT treatment and also at 6 months after treatment completion as shown in figure 1 below. The follow up schedule was thoroughly explained to respondents at recruitment and follow-up visits were scheduled to coincide with patients' drug collection time from GDH. At the time of recruitment, patients' contact details were gathered which included home addresses and two telephone numbers (landline or mobile) belonging either to them, a family member or neighbor to facilitate the follow up process. Follow up reminders were sent through telephone calls. The contact information of the respondents was reviewed at each subsequent visit to aid in efficient follow up. The follow up period was from December 2013 to March 2015.

The first follow up was scheduled at two months after recruitment. The follow up completion rate at this first follow up was 93.4%, with 40 participants lost to follow up. The total number of participants entering the second follow up comprised of 558 PTB patients instead of 574, as 16 participants experienced a treatment outcome, which included 13 deaths and 3 transferred out patients. The follow up completion rate for the second phase was 93.3%, with 37 PTB patients lost to follow up. For the third phase, the completion rate was 93% and 34 patients were lost to follow up. The follow-up completion rate of the fourth phase was 100%; however, the overall follow up completion rate of the 614 PTB patients was 81.9%, with 111 patients lost to follow up. The figure 2 that follows highlights the number of respondents lost to follow up at each phase of the study and also the number who experienced a treatment outcome during and at the end of ATT and also after treatment completion.

The common reasons for lost to follow up included; patients movement to another city, patients in denial of their disease status, patients attributing their signs and symptoms to black magic / super-natural power, patients claiming they were incorrectly diagnosed and the inability to contact the patient through telephone calls and home visits.

Additional data

Interview

Trained male and female data collectors conducted the interviews. Both were employed as full-time data collectors who worked six days a week in the OPD of GDH. Data were collected on structured questionnaires from the study participants at the time of recruitment and at each follow up visit. The variables studied included socio-demographic characteristics such as age, gender, education, occupation, income, area of residence and marital status. Lifestyle and behavioural characteristics, which included smoking status, alcohol consumption status, history of imprisonment, body mass index (BMI) and drug abuse were also determined. Patients clinical presentation variables included cough longer than 3 weeks, prolonged fever, difficulty in breathing, presence of blood in sputum, night sweats, weight loss and type of PTB. Also history of co-morbidities such as hypertension, heart disease, renal disease and asthma was inquired. Other variables studied include type of diabetes, glyceamic control among the diabetics, family history of diabetes, exposure to a household TB contact and adherence to DOTS therapy or not. Information on these variables was collected at baseline and at each subsequent visit. Additionally, at each follow up patients were inquired about adverse effects related to ATT and data was collected on favourable and unfavourable outcome amongst them.

Measurement of height and weight

The height of the PTB patients was measured with a stadiometer to the last complete 0.1cm and rounded to the nearest whole number while patients were standing erect without shoes. The weight of these patients was measured on a standing scale with minimal clothing on to the last 0.1kg and rounded to the nearest whole number. Throughout the study the same instruments were used which were calibrated every day to ensure validity of the results.[19]

Estimation of blood sugar

Patients were inquired about their diabetic status and those who had a known diagnosis of diabetes (self-report) were labeled as diabetic. In those with unknown diabetic status, a random blood glucose (RBG) test was conducted at baseline and a fasting blood glucose (FBG) test was conducted at first follow up visit, which coincided with second month of ATT treatment. (Figure 3) The protocol used to screen TB patients for diabetes in China and India has been adhered to in the study.[20,21,22]

Random blood glucose test

Patients' RBG was estimated using the Accu-Check® Active glucometer by Roche®. All patients having a RBG $\geq$ 110mg/dl were offered FBG testing.

Fasting blood glucose test

Patients were explained to fast overnight i.e 8 hours before coming for their first follow up visit at the second month of ATT. They were reminded of the fast through telephone calls twice before their arrival at the health facility; once a week before their date of visit to the hospital and second call a day before the visit so as to ensure their eligibility for the FBG test. For the FBG estimation the same procedure as mentioned above was carried out. However, before conducting the test patients were again inquired regarding their overnight fast confirming their fasting status. And in case of any suspicion of food intake, the patient was asked to come the next day for

FBG test. Patients having a FBG ≥ 126mg/dl were diagnosed as diabetic, based on WHO guidelines.[23] The diabetics were referred to a specialist for management of their newly diagnosed disease.[22,24]

Sputum smear examination

The diagnosis of PTB patients and assessment of treatment outcomes was established by performing sputum smear microscopy using Ziehl-Nelson (ZN) staining technique by the laboratory staff of GDH under the NTP. Presence of acid-fast bacillus (AFB) was checked in the sputum sample after preparing a sputum smear on a glass slide followed by its staining and fixation. The reporting of AFB was done as is depicted in table 1 below:

Table 1: Reporting AFB through sputum smear microscopy[16]

Seen on slide	Result	Positive (grading)	Bacterial Load
More than 10AFB per field	POS	3+	Heavy
1-10AFB per field	POS	2+	Medium
10-99AFB in 100 fields	POS	1+	Low
1-9 AFB in 100 fields	POS	Record actual number	Very low
No AFB in 100 fields	NEG	0	Nil/ Not seen

The results' of the sputum sample were communicated by the laboratory personnel to OPD staff, who recorded it on the patients' treatment card and in hospitals TB registers for record. The results were acquired by the data collectors of the study from the patient treatment card and verified with the hospital TB registers.

Estimation of glycosylated haemoglobin

At the second follow up visit which coincided with the 5th month of ATT, a blood sample was drawn from all known and the newly diagnosed diabetic PTB patients for the estimation of gylcosylated hemoglobin. The glyceamic assessment was performed at a time when the effect of transient hyperglyceamia due to TB disease was probably negligible. This would provide an unbiased estimate of the association between patients' glyceamic control and treatment outcome. A 3c.c. sample of blood was obtained through venipuncture by the data collectors using a disposable syringe and using aseptic technique. The blood was immediately transferred to an ethylene di-amine tetra acetic acid (EDTA) tube, which was gently inverted to ensure mixing of the components. The specimen was transported on a daily basis to the pathology laboratory of Punjab Institute of Cardiology (PIC), where they were analyzed for hemoglobin A1c (HbA1c) using high performance liquid chromatography (HPLC). A HbA1c value of ≤ 7% was considered as normal value and a HbA1c value >7% was considered as an abnormal value in the study.[25]

Treatment Outcomes

All the patients were followed up to determine treatment outcomes. The standardized treatment outcome definitions given by the NTP, Pakistan and the WHO were used in the study.[26,27] The treatment outcomes included:

Cured: A sputum smear positive patient, who had completed 6 months of treatment and became sputum smear negative at the end of treatment and on at least one previous occasion.

Treatment completed: A sputum smear positive patient, who completed 6 months of treatment and had at least one follow up smear negative result and none at the end of treatment due to any reason or smear negative cases who completed six months of treatment successfully.

Death: A patient who died for any reason during the course of treatment.

Failure: A sputum smear positive patient who remained positive or again became positive at 5 months or a sputum smear negative patient found to be smear positive at the end of 2 months.

Default: A patient whose treatment was interrupted for two consecutive months or more after registration. (According to new definition this treatment outcome is called "Loss to follow up")

Transferred out: A patient who was transferred to another centre and for whom the treatment outcome was not known. (According to new definition this treatment outcome is called "Not Evaluated")

Relapse: A patient who was previously treated for TB, was declared cured or treatment completed at the end of their treatment and was diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).[27]

Treatment outcomes were categorized into favourable and unfavourable treatment outcomes. The "unfavourable outcome" included patients who defaulted, who died, who were transferred out, who had treatment failure and who had relapse. Whereas, the category of "favourable outcome" included patients who were cured and who completed treatment.

The figure 4 below depicts the various data collection activities undertaken by the DITTO study.

Characteristics of the study population

Of the total 661 new PTB patients who fulfilled the inclusion criteria, 614 patients consented to participate in the study, whereas 47 refused participation. The assessment of 614 respondents' diabetic status revealed that 113 (18%) were diabetic and 501 (82%) were non-diabetic. The age distribution of the PTB cohort comprising 113 (18%) diabetics and 501 (82%) non-diabetics shows the diabetic PTB respondents' to be older (mean age=47.4) as compared to the non-diabetic PTB respondents (mean age=28.5) ($p<0.001$). A greater proportion of diabetic PTB patients were illiterate (n=74/113,65.5%) than the non-diabetic PTB patients (n=249/501,50%) (p=0.035) and most PTB diabetics were married (n=101/113, 89%) as opposed to non-diabetic PTB patients (n=243/501,58%) ($p<0.001$). The majority of the exposed PTB patients were overweight (n=18/113,17%) and obese (n=9/113,8%), whereas, majority of un-exposed respondents were underweight (n=289/501,58%). ($p<0.001$). More PTB diabetic patients gave history of heart disease (n=14/113,12%) and hypertension (n=26/113, 23%) as compared to non-diabetic PTB patients (n=2/501,0.4%) and (n=13,501,3%) ($p<0.001$) respectively, as is depicted in table 2 below.

Table 2: Profile of 614 new pulmonary tuberculosis patients with (n=113) or without diabetes mellitus (n= 501) presenting at Gulab Devi Chest Hospital, Lahore

	PTB with Diabetes n=113		PTB without Diabetes n=501		Total n=614	P-value
	n	%	n	%	n (%)	
Age Group (in years)						< 0.001
15-19	1	1	134	27	135 (22)	
20-24	4	3.5	138	27	142 (23)	
25-29	4	3.5	63	13	67 (11)	
30-39	16	14	74	15	90 (15)	
40-49	30	27	37	7	67 (11)	
>50	58	51	55	11	113 (18)	
Gender						0.357
Male	53	47	259	52	312 (51)	
Female	60	53	242	48	302 (49)	
Residence						0.179
Urban	84	74	340	68	424 (69)	
Rural	29	26	161	32	190 (31)	
Educational qualification						0.035
Illiterate	74	65.5	249	50	323 (52)	
Primary	13	11.5	71	14	84 (14)	
Matriculation	20	18	126	25	146 (24)	
Intermediate	5	4	25	5	30 (5)	
Bachelors	1	1	17	3	18 (3)	
Masters and above	0	0	13	3	13 (2)	
Income Category (Rupees)						0.113
Nil‡	73	65	311	62	384 (63)	
<5000	5	5	38	8	43 (7)	
5100-8000	6	5	61	12	67 (11)	
8100-11000	10	9	44	9	54 (9)	
11100-14000	7	6	19	4	26 (4)	
14100-17000	6	5	15	3	21 (3)	
>17100	6	5	13	2	19 (3)	
Marital status						<0.001
Married	101	89	243	48.4	344 (56)	
Single	12	11	255	51	267 (43.5)	
Divorced	0	0	1	0.2	1 (0.2)	
Widowed	0	0	2	0.4	2 (0.3)	
BMI*						<0.001
Less than 18.50	18	17	289	58	307 (51)	
18.50 – 24.99	63	58	194	39	257 (42)	
25 – 29.99	18	17	9	2	27 (4)	
30 and above	9	8	8	1	17 (3)	
Heart disease						<0.001
Yes	14	12	2	0.4	16 (3)	

No	99	88	499	99.6	598 (97)	
Hypertension						<0.001
Yes	26	23	13	3	39 (6)	
No	87	77	488	97	575 (94)	

‡Income in the form of loans/ help from relatives/extended family/friends
* Body mass index, of 608 patients

Findings to date

The treatment outcome analyzed as a binary variable shows 69 (14%) patients had an unfavourable outcome and 434 (86%) had a favourable outcome. In univariate analysis, patients with diabetes were more likely to experience an unfavourable outcome than patients without diabetes (OR=2.6, 95% CI: 1.48 to 4.56,p = 0.001). Other studies conducted in Taiwan and South Korea have also reported an increased risk of unfavourable treatment outcome among diabetic PTB patients as compared to non-diabetic PTB patients i.e an OR of 1.46 (95% CI of 1.03 to 2.08)[28] and 1.78 (95% CI= 1.07 to 2.95)[29] respectively.

Strengths and weaknesses

The strengths of our study included employing a rigorous study design i.e the prospective cohort study design, which generates valid results as opposed to other observational epidemiological study designs in our endeavour to determine treatment outcomes among tuberculosis diabetic patients. The data collection tool gathered information on all possible confounders identified through literature review and having biological plausibility. These confounders will thus be adjusted for in the analysis producing valid results. The exposure status of PTB patients' was based upon two tests; one random and the other fasting blood glucose test. The confirmatory FBG test was conducted two months after initiation of ATT to rule out the bias associated with transient stress induced hyperglycemia attributed to tuberculosis disease. Lastly, standardized treatment outcome definitions provided by WHO were used in the study. To our knowledge, no previous study has been conducted in Pakistan to determine the effect of diabetes on treatment outcome of TB patients.

The study found it beneficial to employ both a male and a female data collector who were trained for gender matched data collection considering the prevailing cultural environment. We ensured negligible data collector turnover, which helped develop a good rapport between the researcher and respondents. Additionally, we provided a 24 hour helpline, which was very popular among the patients, was greatly appreciated by them and helped develop sustained relationships with them; maximizing response rate.

However, there were certain limitations in our study. The drug susceptibility testing was not done among the PTB cohort at the time of enrollment or during the course of ATT, which could have led to bias in the results. However because of our inclusion criteria of recruiting only the new PTB patients, with no prior history of ATT intake drug resistance may not be an issue. The difference in drug resistance patterns between the two groups was unlikely to have contributed to the observed results.

Secondly, HIV status, which has been identified as a strong risk factor for adverse treatment outcome among TB patients, was not determined. Lastly, we were unable to study the effect of glucose control on TB treatment outcome as HbA1c values for the entire cohort were not available. Due to resource constraints glycosylated hemoglobin blood analyses was performed of only the diabetics in the study. If treatment outcome among diabetic PTB patients is modified by glucose control, our results could be affected. However, according to Mi F et al, 2 month and 6 month FBG levels among PTB patients did not have statistically significant association with adverse outcomes.[30]

Collaboration

The data is not available freely, however we welcome specific and detailed proposals for collaboration. Enquiries and requests for further information should be made to fatimamukhtar@doctor.com

Authors' Contributions: FM contributed to conception and design of the work, acquisition, analysis and interpretation of data and write up. ZAB contributed to conception of work, analysis of data, revised the work for intellectual content and approved the final version to be published.

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Figure 1: Follow up schedule of PTB patients on ATT at Gulab Devi Hospital, Lahore

Figure 2: Flow diagram depicting the follow up periods of the PTB cohort along with treatment outcome and loss to follow up at Gulab Devi Chest Hospital, Lahore

Figure 3: The protocol used in screening PTB patients for diabetes

Figure 4: Flow diagram of data collection activity at Gulab Devi Hospital, Lahore

Figure 1: Follow up schedule of PTB patients on ATT at Gulab Devi Hospital, Lahore

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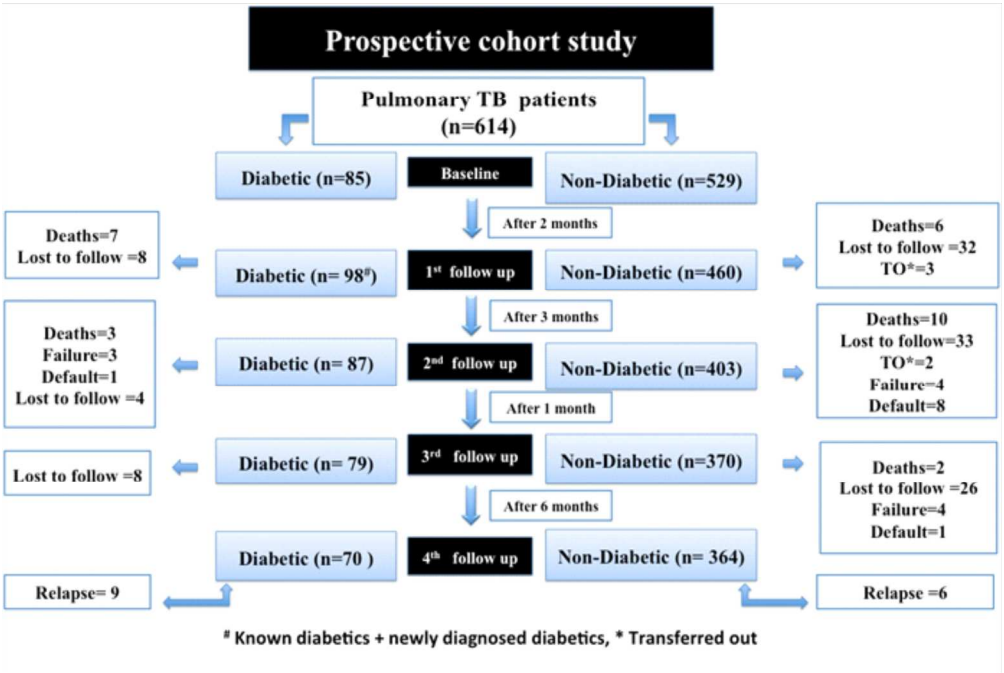

Figure 2: Flow diagram depicting the follow up periods of the PTB cohort along with treatment outcome and loss to follow up at Gulab Devi Chest Hospital, Lahore

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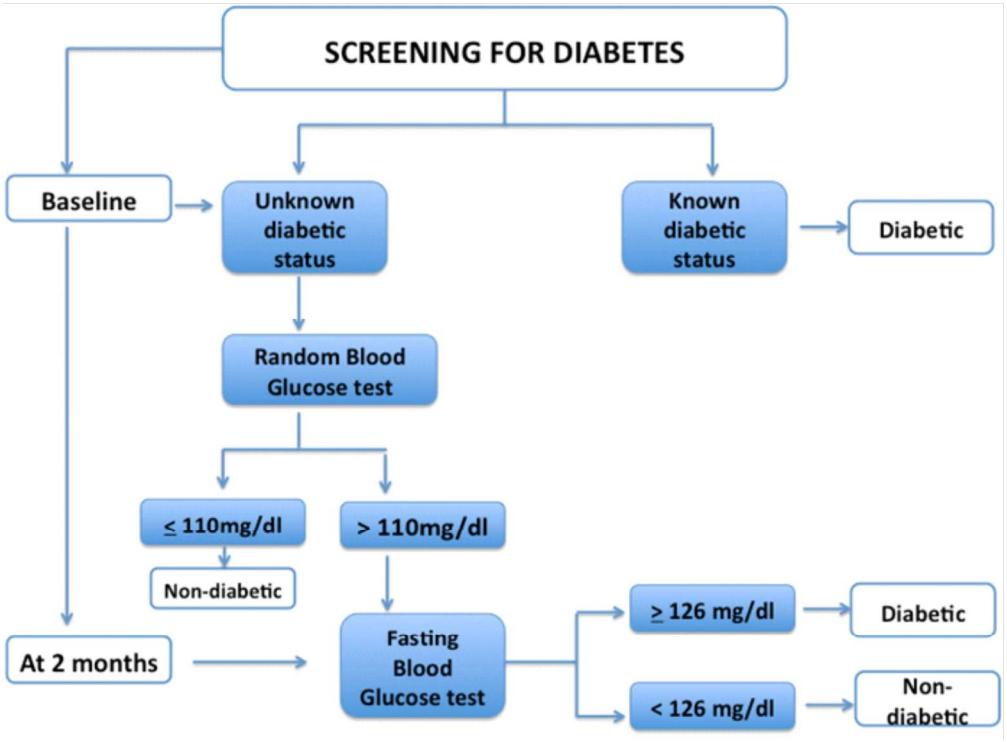

Figure 3: The protocol used in screening PTB patients for diabetes

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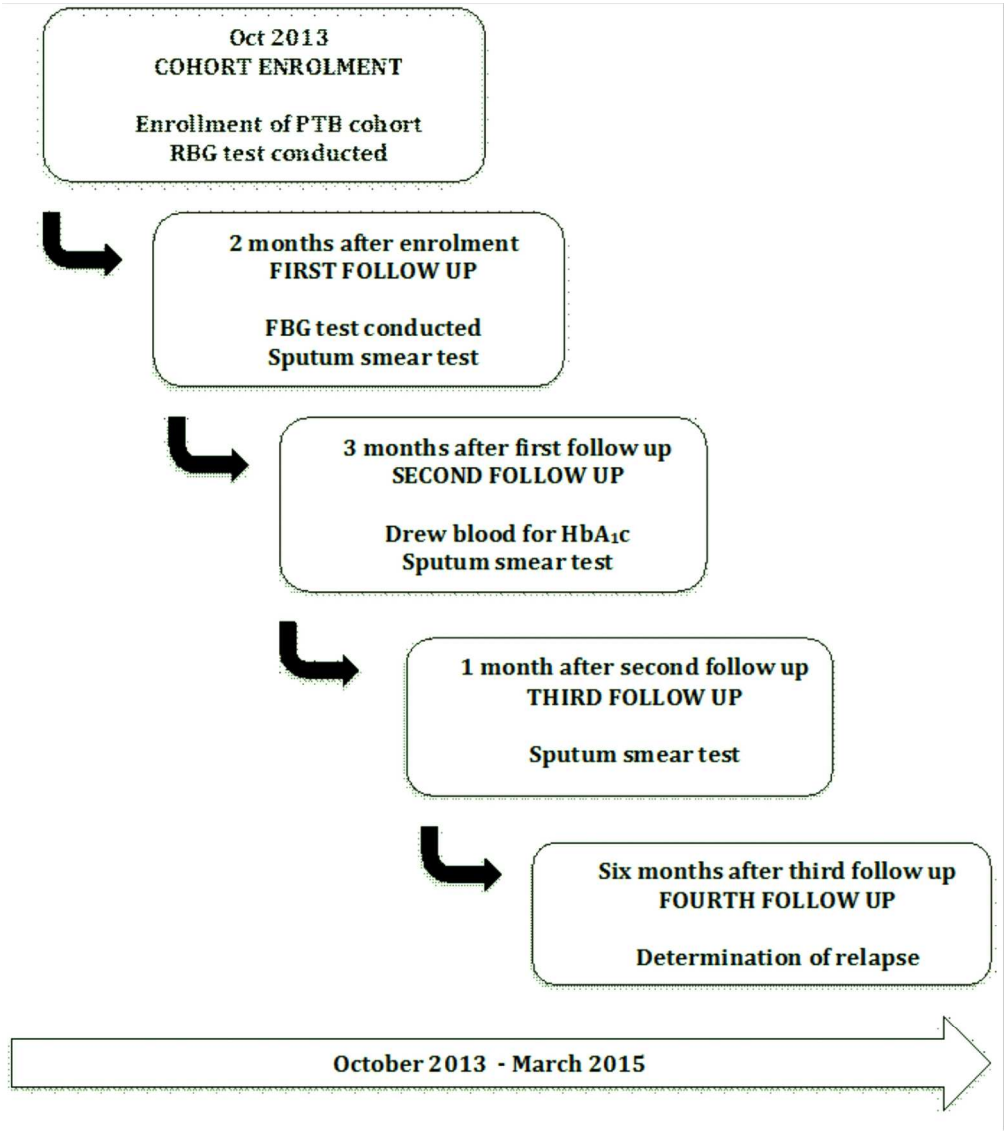

Figure 4: Flow diagram of data collection activity at Gulab Devi Hospital, Lahore

245x276mm (300 x 300 DPI)

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Cohort profile: the diabetes-tuberculosis treatment outcome (DITTO) study in Pakistan

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Cohort profile: the diabetes-tuberculosis treatment outcome (DITTO) study in Pakistan

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Abstract

Purpose: Pakistan is faced with an increasing prevalence of diabetes in addition to its existing high burden of tuberculosis. Diabetes has a detrimental effect on treatment outcomes of tuberculosis patients, which may hinder achieving the goals of the End-TB strategy by 2030. We conducted a prospective cohort study to determine difference between treatment outcomes among diabetic and non-diabetic new pulmonary tuberculosis patients. This would help generate contextual and valid scientific evidence from a developing country like ours with its unique interplay of socio- cultural, economic and health system factors, to inform policy and practice.

Participants: This paper outlines the baseline characteristics of 614 new cases of pulmonary tuberculosis (PTB) aged 15 years and older, which were followed up prospectively at the 2nd, 5th and 6th month while on anti-tuberculosis treatment and 6 months after treatment completion.

Findings to date: We ascertained patients' diabetic status by conducting random and fasting blood glucose tests and their glycemic control by determining glycosylated hemoglobin. Treatment outcomes were established using standardized definitions provided by World Health Organization. The assessment of 614 respondents' diabetic status revealed that 113 (18%) were diabetic and 501 (82%) were non-diabetic. A greater proportion of diabetic PTB patients were illiterate (n=74/113, 65.5%) as compared to non-diabetic PTB patients (n=249/501,50%) (p=0.035). More PTB diabetic patients gave history of heart disease (n=14/113,12%) and hypertension (n=26/113, 23%) as compared to non-diabetic PTB patients (n=2/501,0.4%[heart disease] andn=13,501, 3%[hypertension]) (p<0.001). Unfavourable treatment outcome was more likely among diabetic PTB patients (n=23/93,25%) as opposed to non-diabetic PTB patients (n=46/410,11%)(p=0.001).

Future plans: We are negotiating with the government regarding funding for a further two year follow up of the cohort to ascertain death and relapse in the post treatment period; and also differentiate between re-infection and recurrence among these patients with respect to their diabetic status.

Strengths and Limitations of this study

- The diabetes tuberculosis treatment outcome (DITTO) study is the first prospective cohort studywhich has been conducted in Pakistan to determine the effect of diabetes on treatment outcome of TB patients.
- The ascertainment of diabetic status of DITTO cohort was based upon two tests; one random and the other fasting blood glucose test.
- The main limitations are the inability to conduct drug susceptibility testing of patients and to determine their HIV status at the time of recruitment into the DITTO cohort due to non-availability of funds.

Introduction

There is a resurgence of interest in the dual epidemic of diabetes and tuberculosis with the global increase in the diabetic population. This converging epidemic of diabetes and tuberculosis has many untoward and detrimental effects.[1] The risk of development of tuberculosis is tripled by diabetes.[2] It increases the severity related to tuberculosis and also slows the response to tuberculosis treatment.[3] The clearance of tuberculosis mycobacterium from the sputum, which is required to declare the patient noninfectious, is also delayed by diabetes.[4] Diabetes increases the risk of treatment failure, death, and relapse among patients with tuberculosis, which poses a challenge for both the developed and developing world.[1,5]

Low and middle income countries like Pakistan are likely to be affected the most as they are struggling with their existing high burden of tuberculosis and the growing population of diabetics. Pakistan ranks 4th in terms of global burden of TB with 630,000 cases and an estimated incidence of 231 cases per 100,000 population.[6,7] Pakistan is one of the 10 countries with the highest number of diabetic patients and a prevalence ranging from 7.6% to 11%.[8,9] It is feared that diabetes mellitus co-morbidity will hinder the achievement of the long-term goal of eliminating tuberculosis. Tuberculosis will be considered eliminated if by the year 2050 there is less than one incident case of the disease per one million population.[3,10]

Most of the scientific knowledge regarding association between diabetes and tuberculosis has been generated in industrialized countries.[11] However, recently China and India have made valuable contributions.[12,13] Currently, the published literature suffers from certain limitations. The majority of studies are either cross-sectional, case control or retrospective cohort studies. The ascertainment of patient's diabetic status is based on past records and a substantial number of studies fail to control for important confounders.[5,14,15] Furthermore, good quality evidence needs to be generated from developing countries which can help in addressing this problem. Pakistan has a high burden of tuberculosis and a rapidly growing population of diabetics. Data are scarce regarding the impact of diabetes on tuberculosis treatment outcome in Pakistan. Therefore, this prospective cohort study was undertaken to determine the difference between treatment outcomes in diabetic and non-diabetic patients of pulmonary tuberculosis and identify the determinants of treatment outcomes in patients of pulmonary tuberculosis with and without diabetes mellitus.

Cohort Description

The recruitment and enrollment of new adult cases of pulmonary TB (PTB) that were diagnosed, registered and received complete treatment at Gulab Devi Chest Hospital (GDH), Lahore began in October 2013. The diagnosis of PTB, both sputum smear positive and sputum smear negative was made according to the definition given by the National Tuberculosis Control Program (NTP).[16] According to NTP a patient having one or two sputum samples positive for AFB, is labeled as sputum smear positive PTB patient. If both sputum samples are found negative, an antibiotic course of 7 days is prescribed to the patient. After 7 days, based on doctors assessment of the patient an X Ray chest if required is conducted, which if compatible with active pulmonary TB helps declare the patient sputum smear negative PTB. A new case was a PTB patient, sputum smear positive or sputum smear negative who had never taken

TB drugs in the past, or had taken TB drugs for less than 4 weeks in the past but was not registered with the National Tuberculosis Control Program (NTP). An adult was a PTB patient aged 15 years or older.[16] Patients with previous history of anti-tuberculosis treatment (ATT), who were not sure or were unable to recall previous therapy with ATT and who were severely ill, disabled or mentally ill were excluded from participation in the study. All eligible PTB patients willing to participate after giving informed written consent were enrolled in the study cohort.

The enrolment period lasted up to March 2014, till our sample size of 614 participants was successfully achieved. We recruited 614 PTB patients based on our statistical calculations for cohort studies using WHO software for sample size calculation in health studies.[17] The enrolled PTB patients' diabetic status was ascertained. The diabetic PTB and the non-diabetic PTB patients were followed up prospectively, while on standardized Category I treatment consisting of fixed dose combinations for adults in accordance with current guidelines of NTP.[18] The intensive phase of treatment was of two months in which Rifampicin, Isoniazid, Ethambutol and Pyrazinamide was given to all patients on a daily basis. This was followed by a continuation phase of four months in which a daily dose of Isoniazid and Rifampicin was given to all patients.

Follow Up

The two groups comprising of exposed (diabetic) PTB patients and unexposed (non-diabetic) patients were followed up prospectively at 2nd, 5th and 6th months of ATT treatment and also at 6 months after treatment completion. The follow up schedule was thoroughly explained to respondents at recruitment and follow-up visits were scheduled to coincide with patients' drug collection time from GDH. At the time of recruitment, patients' contact details were gathered which included home addresses and two telephone numbers (landline or mobile) belonging either to them or a family member or neighbor to facilitate the follow up process. Follow up reminders were sent through telephone calls. The contact information of the respondents was reviewed at each subsequent visit to aid in efficient follow up. The follow up period was from December 2013 to March 2015.

The first follow up was scheduled at two months after recruitment. The follow up completion rate at this first follow up was 93.4%, with 40 participants lost to follow up. The total number of participants entering the second follow up comprised of 558 PTB patients instead of 574, as 16 participants experienced a treatment outcome (13 deaths and 3 transferred out patients). The follow up completion rate for the second phase was 93.3% with 37 PTB patients lost to follow up. For the third phase, the completion rate was 93% and 34 patients were lost to follow up. The follow-up completion rate of the fourth phase was 100%; however, the overall follow up completion rate of the 614 PTB patients was 81.9% with 111 patients lost to follow up. Figure 1 highlights the number of respondents lost to follow up at each phase of the study and also the number who experienced a treatment outcome during and at the end of ATT and also after treatment completion.

The common reasons for lost to follow up included; patients movement to another city, patients in denial of their disease status, patients attributing their signs and symptoms to black magic / super-natural power, patients claiming they were

incorrectly diagnosed and the inability to contact the patient through telephone calls and home visits.

Additional data

Interview

Trained male and female data collectors conducted the interviews. They were employed as full-time data collectors who worked six days a week in the OPD of GDH. Data were collected on structured questionnaires from the study participants at the time of recruitment and at each follow up visit. The variables studied included socio-demographic characteristics such as age, gender, education, occupation, income, area of residence and marital status. Lifestyle and behavioural characteristics, which included smoking status, alcohol consumption status, history of imprisonment, body mass index (BMI) and drug abuse were also determined. Patients clinical presentation variables included cough longer than 3 weeks, prolonged fever, difficulty in breathing, presence of blood in sputum, night sweats, weight loss and type of PTB. Also, history of co-morbidities such as hypertension, heart disease, renal disease and asthma was inquired. Other variables studied were type of diabetes, glyceamic control among the diabetics, family history of diabetes, exposure to a household TB contact and adherence to DOTS therapy . Information on these variables was collected at baseline and at each subsequent visit. Additionally, at each follow up patients were inquired about adverse effects related to ATT and data were collected on favourable and unfavourable outcome amongst them.

Measurement of height and weight

The height of the PTB patients was measured with a stadiometer to the last complete 0.1cm and rounded to the nearest whole number while patients were standing erect without shoes. The weight of these patients was measured on a standing scale with minimal clothing on to the last 0.1kg and rounded to the nearest whole number. Throughout the study the same instruments were used which were calibrated every day to ensure validity of the results.[19]

Estimation of blood sugar

Patients were inquired about their diabetic status and those who had a known diagnosis of diabetes (self-report) were labeled as diabetic. In those with unknown diabetic status, a random blood glucose (RBG) test was conducted at baseline and a fasting blood glucose (FBG) test was conducted at first follow up visit, which coincided with second month of ATT treatment (Figure 2). The protocol used to screen TB patients for diabetes in China and India has been adhered to in this study.[20,21,22]

Random blood glucose test

Patients' RBG was estimated using the Accu-Check® Active glucometer by Roche®. All patients having a RBG above the cut-off value were offered FBG testing.

Fasting blood glucose test

Patients were explained to fast overnight i.e 8 hours before coming for their first follow up visit at the second month of ATT. They were reminded of the fast through telephone calls twice before their arrival at the health facility; first call a week before their date of visit to the hospital and the second call a day before the visit to ensure

their eligibility for the FBG test. For FBG estimation, the same procedure mentioned above was carried out. However, before conducting the test patients were again inquired regarding their overnight fast confirming their fasting status. In case of any suspicion of food intake, the patient was asked to come the next day for FBG test. Patients' diagnosis of diabetes was based on WHO guidelines.[23] The diabetics were referred to a specialist for management of their newly diagnosed disease.[22,24]

Sputum smear examination

The diagnosis of PTB patients and assessment of treatment outcomes was established by performing sputum smear microscopy using Ziehl-Nelson (ZN) staining technique by the laboratory staff of GDH under the NTP. Presence of acid-fast bacillus (AFB) was checked in the sputum sample after preparing a sputum smear on a glass slide followed by its staining and fixation. The reporting of AFB was done as depicted in table 1 .

Table 1: Reporting AFB through sputum smear microscopy[16]

Seen on slide	Result	Positive (grading)	Bacterial Load
More than 10AFB per field	POS	3+	Heavy
1-10AFB per field	POS	2+	Medium
10-99AFB in 100 fields	POS	1+	Low
1-9 AFB in 100 fields	POS	Record actual number	Very low
No AFB in 100 fields	NEG	0	Nil/ Not seen

The results of the sputum sample were communicated by the laboratory personnel to OPD staff, who recorded it on the patients' treatment card and in hospitals TB registers. The results were acquired by the data collectors of the study from the patient treatment card and verified with the hospital TB registers.

Estimation of glycosylated haemoglobin

At the second follow up visit which coincided with the 5th month of ATT, a blood sample was drawn from all known and the newly diagnosed diabetic PTB patients for the estimation of gylcosylated hemoglobin. The glyceamic assessment was performed at a time when the effect of transient hyperglyceamia due to TB disease was probably negligible. This would provide an unbiased estimate of the association between patients' glyceamic control and treatment outcome. A 3c.c. sample of blood was obtained through venipuncture by the data collectors using a disposable syringe and using aseptic technique. The blood was immediately transferred to an ethylene di-amine tetra acetic acid (EDTA) tube, which was gently inverted to ensure mixing of the components. The specimen was transported on a daily basis to the pathology laboratory of Punjab Institute of Cardiology (PIC), where they were analyzed for hemoglobin A1c (HbA1c) using high performance liquid chromatography (HPLC). A HbA1c value of $\leq$ 7% was considered as normal value and a HbA1c value >7% was considered as an abnormal value in the study.[25]

Treatment Outcomes

All the patients were followed up to determine treatment outcomes. The standardized treatment outcome definitions given by the NTP, Pakistan and the WHO were used in the study.[26,27] The treatment outcomes included:

Cured: A sputum smear positive patient, who had completed 6 months of treatment and became sputum smear negative at the end of treatment and on at least one previous occasion.

Treatment completed: A sputum smear positive patient, who completed 6 months of treatment and had at least one follow up smear negative result and none at the end of treatment due to any reason or smear negative cases who completed six months of treatment successfully.

Death: A patient who died for any reason during the course of treatment.

Failure: A sputum smear positive patient who remained positive or again became positive at 5 months or a sputum smear negative patient found to be smear positive at the end of 2 months.

Default: A patient whose treatment was interrupted for two consecutive months or more after registration. (According to new definition this treatment outcome is called "Loss to follow up")

Transferred out: A patient who was transferred to another centre and for whom the treatment outcome was not known. (According to new definition this treatment outcome is called "Not Evaluated")

Relapse: A patient who was previously treated for TB, was declared cured or treatment completed at the end of their treatment and was diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).[27]

Treatment outcomes were categorized into favourable and unfavourable treatment outcomes. The "unfavourable outcome" included patients who: defaulted, died, were transferred out, had treatment failure and had relapse. The category of "favourable outcome" included patients who: were cured and completed treatment.

The various data collection activities undertaken by the DITTO study are depicted in Figure 3.

Characteristics of the study population

Out of the total 661 new PTB patients who fulfilled the inclusion criteria, 614 patients consented to participate in the study, whereas 47 refused participation. The assessment of 614 respondents' diabetic status revealed that 113 (18%) were diabetic and 501 (82%) were non-diabetic. The age distribution of the PTB cohort comprising of 113 (18%) diabetics and 501 (82%) non-diabetics shows the diabetic PTB respondents' to be older (mean age=47.4) as compared to the non-diabetic PTB respondents (mean age=28.5) ($p<0.001$). A greater proportion of diabetic PTB patients were illiterate (n=74/113,65.5%) as compared to non-diabetic PTB patients (n=249/501,50%) (p=0.035). The majority of PTB diabetics were married (n=101/113, 89%) as opposed to non-diabetic PTB patients (n=243/501,58%) ($p<0.001$). The majority of the exposed PTB patients were overweight (n=18/113,17%) and obese (n=9/113,8%), whereas, majority of un-exposed respondents were underweight (n=289/501,58%)($p<0.001$). More PTB diabetic patients gave history of heart disease (n=14/113,12%) and hypertension (n=26/113, 23%) as compared to non-diabetic PTB patients (n=2/501,0.4%) and (n=13,501,3%) ($p<0.001$) respectively(table 2).

Table 2: Profile of 614 new pulmonary tuberculosis patients with (n=113) or without diabetes mellitus (n= 501) presenting at Gulab Devi Chest Hospital, Lahore

	PTB with Diabetes n=113		PTB without Diabetes n=501		Total n=614	P-value
	n	%	n	%	n (%)	
Age Group (in years)						< 0.001
15-19	1	1	134	27	135 (22)	
20-24	4	3.5	138	27	142 (23)	
25-29	4	3.5	63	13	67 (11)	
30-39	16	14	74	15	90 (15)	
40-49	30	27	37	7	67 (11)	
>50	58	51	55	11	113 (18)	
Gender						0.357
Male	53	47	259	52	312 (51)	
Female	60	53	242	48	302 (49)	
Sputum smear status						0.232
Positive	67	59	266	53	333 (54)	
Negative	46	41	235	47	281 (46)	
Residence						0.179
Urban	84	74	340	68	424 (69)	
Rural	29	26	161	32	190 (31)	
Educational qualification						0.035
Illiterate	74	65.5	249	50	323 (52)	
Primary	13	11.5	71	14	84 (14)	
Matriculation	20	18	126	25	146 (24)	
Intermediate	5	4	25	5	30 (5)	
Bachelors	1	1	17	3	18 (3)	
Masters and above	0	0	13	3	13 (2)	
Income Category (Rupees)						0.113
Nil‡	73	65	311	62	384 (63)	
<5000	5	5	38	8	43 (7)	
5100-8000	6	5	61	12	67 (11)	
8100-11000	10	9	44	9	54 (9)	
11100-14000	7	6	19	4	26 (4)	
14100-17000	6	5	15	3	21 (3)	
>17100	6	5	13	2	19 (3)	
Marital status						<0.001
Married	101	89	243	48.4	344 (56)	
Single	12	11	255	51	267 (43.5)	
Divorced	0	0	1	0.2	1 (0.2)	
Widowed	0	0	2	0.4	2 (0.3)	
BMI*						<0.001
Less than 18.50	18	17	289	58	307 (51)	
18.50 – 24.99	63	58	194	39	257 (42)	
25 – 29.99	18	17	9	2	27 (4)	

30 and above	9	8	8	1	17 (3)	
Heart disease						<0.001
Yes	14	12	2	0.4	16 (3)	
No	99	88	499	99.6	598 (97)	
Hypertension						<0.001
Yes	26	23	13	3	39 (6)	
No	87	77	488	97	575 (94)	

‡Income in the form of loans/ help from relatives/extended family/friends

* Body mass index, of 608 patients

Findings to date

The treatment outcome analyzed as a binary variable shows 69 (14%) patients had an unfavourable outcome and 434 (86%) had a favourable outcome. In univariate logistic regression analysis, patients with diabetes were more likely to experience an unfavourable outcome than patients without diabetes (OR=2.6, 95% CI: 1.48 to 4.56,p = 0.001). Other studies conducted in Taiwan and South Korea have also reported an increased risk of unfavourable treatment outcome among diabetic PTB patients as compared to non-diabetic PTB patients i.e an OR of 1.46 (95% CI of 1.03 to 2.08)[28] and 1.78 (95% CI= 1.07 to 2.95)[29] respectively.

Strengths and weaknesses

The strengths of our study included employing a rigorous study design i.e the prospective cohort study design, which generates valid results as opposed to other observational epidemiological study designs in our endeavour to determine treatment outcomes among tuberculosis diabetic patients. The data collection tool gathered information on all possible confounders identified through literature review and having biological plausibility. These confounders will thus be adjusted for in the analysis producing valid results. The exposure status of PTB patients' was based upon two tests; one random and the other fasting blood glucose test. The confirmatory FBG test was conducted two months after initiation of ATT to rule out the bias associated with transient stress induced hyperglycemia attributed to tuberculosis . Lastly, standardized treatment outcome definitions provided by WHO were used in the study. To our knowledge, no previous study has been conducted in Pakistan to determine the effect of diabetes on treatment outcome of TB patients.

The study found it beneficial to employ both a male and a female data collector who were trained for gender matched data collection considering the prevailing cultural environment. We ensured negligible data collector turnover, which helped develop a good rapport between the researcher and respondents. Additionally, we provided a 24 hour helpline, which was very popular among the patients. It was greatly appreciated by them and helped develop sustained relationships with them thus maximizing our response rate.

However, there were certain limitations in our study. The drug susceptibility testing was not done among the PTB cohort at the time of enrollment or during the course of ATT, which could have led to bias in the results. However, because of our inclusion

criteria of recruiting only the new PTB patients with no prior history of ATT intake, drug resistance may not be an issue. The difference in drug resistance patterns between the two groups was unlikely to have contributed to the observed results. Secondly, HIV statuswhich has been identified as a strong risk factor for adverse treatment outcome among TB patients was not determined. Lastly, we were unable to study the effect of glucose control on TB treatment outcome as HbA1c values for the entire cohort were not available. Due to resource constraints glycosylated hemoglobin blood analyses was performed on only the diabetics in the study. If treatment outcome among diabetic PTB patients is modified by glucose control, our results could be affected. However, according to Mi F et al, 2 months and 6 months FBG levels among PTB patients did not have statistically significant association with adverse outcomes.[30]

Collaboration

The data is not available freely; however, we welcome specific and detailed proposals for collaboration. Enquiries and requests for further information should be made to fatimamukhtar@doctor.com

Authors' Contributions: FM contributed to conception and design of the work, acquisition, analysis and interpretation of data and write up. ZAB contributed to conception of work, analysis of data, revised the work for intellectual content and approved the final version to be published.

Competing interests: None declared.

Ethics Approval: Ethical approval was obtained from the Institutional Ethical Review Committee of Health Services Academy, Islamabad on 17th September 2013. (F.No. -107/2013-IERC/HSA). Permission was also taken from the administration of the Gulab Devi Chest Hospital, Lahore where data collection was undertaken. All patients gave written informed consent before recruitment in the study.

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Figure 1: Flow diagram depicting the follow up periods of the PTB cohort along with treatment outcome and loss to follow up at Gulab Devi Chest Hospital, Lahore

Figure 2: The protocol used in screening PTB patients for diabetes

Figure 3: Flow diagram of data collection activity at Gulab Devi Hospital, Lahore

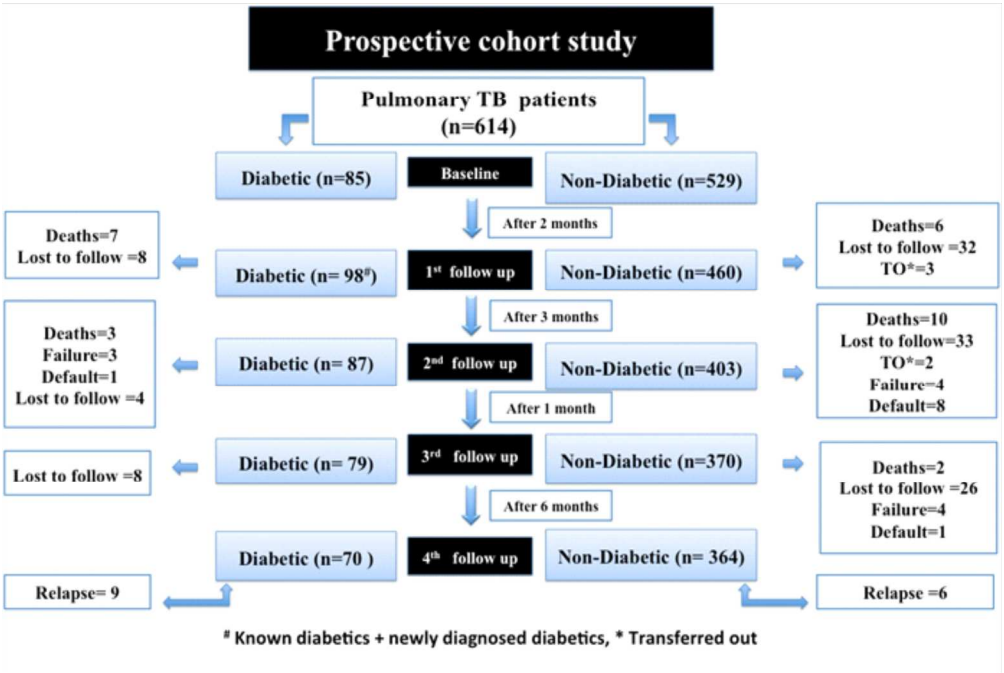

Figure 1: Flow diagram depicting the follow up periods of the PTB cohort along with treatment outcome and loss to follow up at Gulab Devi Chest Hospital, Lahore

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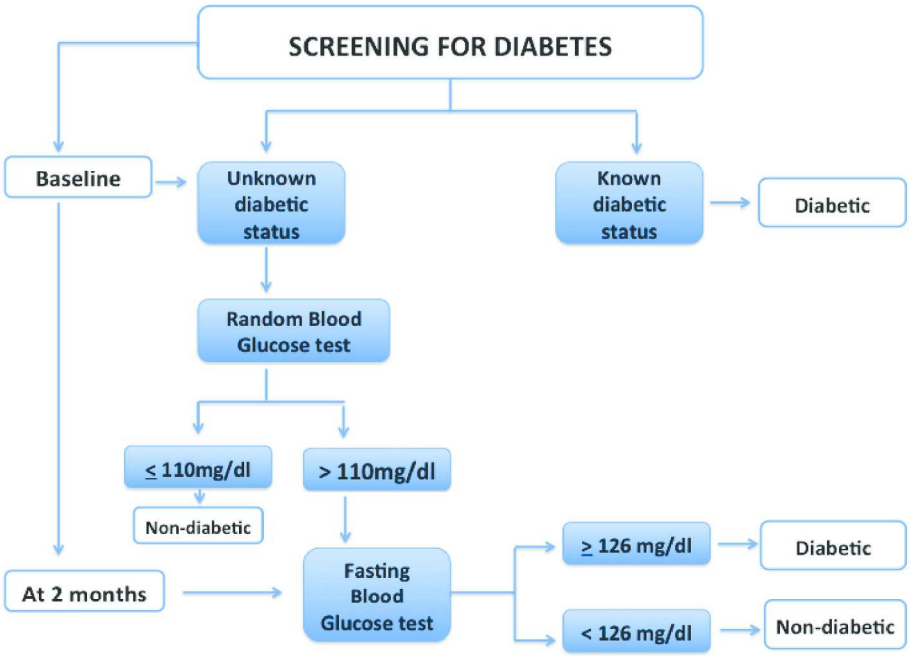

Figure 2: The protocol used in screening PTB patients for diabetes

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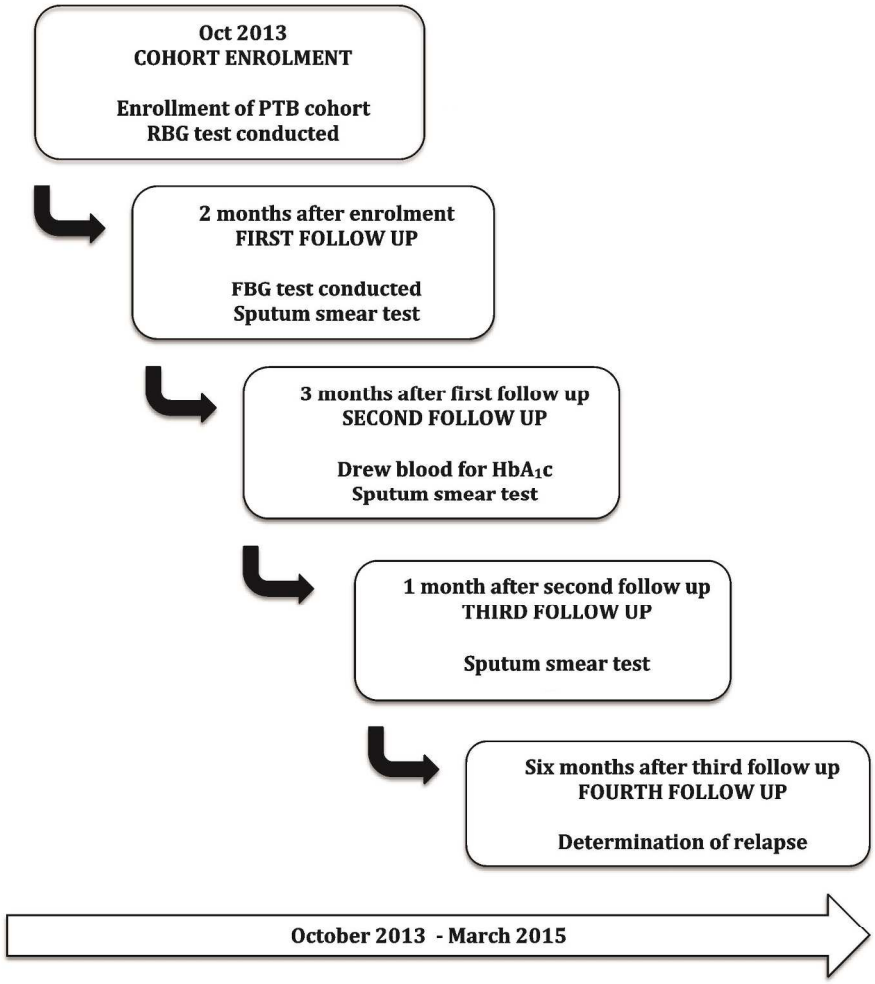

Figure 3: Flow diagram of data collection activity at Gulab Devi Hospital, Lahore

209x224mm (300 x 300 DPI)