Screening for Diabetes Mellitus in Patients Diagnosed with Pulmonary Tuberculosis

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Abstract

Background: The epidemic of diabetes mellitus (DM) poses a threat for global tuberculosis (TB) control.

Objective: This study attempts to assess the value of screening for diabetes in patients with pulmonary tuberculosis and reviews the disease burden, clinical and radiographic manifestations, rates of sputum smear positivity and time to conversion, treatment outcomes and fatality rates, in the local setting.

Methods: This is a prospective observational cohort study involving adults diagnosed with pulmonary tuberculosis at the PTSI TB DOTS out-patient clinic, regardless of sputum-smear status, from July 2011-November 2012. A diabetes screening tool was used and patients were screened for presence of DM. Treatment outcomes were also determined.

Results: Of the 38 patients enrolled, seven (18.4%, 95% confidence interval 7.7-34.3) were diagnosed with DM. This is higher than the estimated 12.9% in 2010 and 14.4% projected estimate in 2030 in our country by a report of WHO as well as in reported prevalence of DM among patients with PTB in large studies done in China (12.4%) and India (13%). There was no significant difference noted in the basic profile, clinical and radiographic presentation, sputum conversion and treatment outcomes among patients with DM and without DM who were being treated for PTB.

Conclusion: This study demonstrates the value and feasibility of screening for DM among patients with PTB. Although the findings of this study are consistent with most of previous similar studies, the estimate on the true prevalence of DM may not be very accurate because of the small sample size. Hence, a multi-center study with a larger sample size must be conducted to more accurately measure the true prevalence of DM among patients with TB and to determine associations of various clinical and radiographic presentations and clinical outcomes.

Keywords: diabetes mellitus, pulmonary tuberculosis, screening

Introduction

There is an enormous global burden of disease from diabetes mellitus (DM) and tuberculosis (TB).[1] Tuberculosis is estimated to infect one-third of the world's population and cause disease in 8.8 million people per year, and to result in death in 1.6 million people affected.[2] In 2007, there were an estimated 14.4 million people living with TB, 9.2 million new cases and 1.7 million deaths. In 2010, there was an estimated 285 million people living with DM with approximately four million deaths.[1] The global burden of DM is expected to rise from an estimated 180 million prevalent cases currently to a predicted 366 million by 2030.[3]

Concerns have been raised about the twin epidemics of TB and DM especially in countries such as China and India where the prevalence of DM is steadily increasing and the burden of TB is immense.[2] The steadily growing epidemic of DM poses a threat for global TB Control.[1]

Numerous studies have been made to determine the association between these two diseases. A recent meta-analysis shows that DM increases the risk of active TB, regardless of different study designs, background TB incidence, or geographic region of the study.[3] However, these studies have limitations since very few were carried out in low-income countries raising uncertainty about the strength of the DM–TB association in these settings, and many critical questions remain unanswered.[1]

In an attempt to address questions and uncertainties regarding the association of DM and TB, a systematic review was conducted in May 2009, the findings of which were presented in an expert meeting in November 2009 at the International Union Against Tuberculosis and Lung Disease. The objectives of the meeting were to determine if there was enough evidence to create policy recommendations regarding the diagnosis and treatment of both diseases, to identify research gaps and to develop

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a research agenda to address these gaps. Ten key research questions were identified, of which, four were selected as high priority: (i) whether, when and how to screen for TB in patients with DM and vice versa (bi-directional screening); (ii) to determine the impact of DM and non-DM hyperglycaemia on TB treatment outcomes and deaths; (iii) and the development of strategies to improve outcomes.[1]

One of the research questions identified was to investigate the value and method of screening for DM in patients with TB. This study therefore attempts to answer this question by verifying the impact of screening for DM in patients with Pulmonary TB (PTB).

Research question:

What is the value of screening for DM in patients with PTB in terms of disease burden, clinical and radiographic manifestations, rates of sputum smear positivity and time to conversion, treatment outcomes and fatality rates?

Objectives

General:

Determine the impact of screening for DM in patients diagnosed with PTB.

Specific:

1. Determine the prevalence of DM in patients diagnosed and being treated for PTB.
2. Determine the clinical and radiographic presentation of PTB in patients with DM.
3. Determine the proportion of patients with sputum smear positive TB and time to sputum conversion in patients proven to have DM.
4. Determine treatment outcomes, including fatality rates, for PTB in patients with DM.

Review of Related Literature

Diabetes as a risk factor for Tuberculosis

Among several risk factors for TB, which include HIV/AIDS, silicosis, malnutrition, alcoholism and smoking, DM has received recent recognition.[1] However, the association between DM and TB has been observed by clinicians since the early part of the 20th century. Several studies have suggested that DM increases the risk of active TB. However, they were often unable to determine whether DM caused TB or whether TB led to the clinical manifestations of DM.[4]

In the meta-analysis of Jeon et al., cohort studies reveal that compared with people who do not have diabetes, people with diabetes have an approximately threefold risk of developing active TB. Higher increases in risk were seen among younger people, in populations with high background TB incidence, and in non-North American populations.[4] In India, diabetes accounts for 14.8% (uncertainty range 7.1% to 23.8%) of PTB and 20.2% (8.3% to 41.9%) of smear-positive (i.e. infectious) tuberculosis.[5] In another study, also done in India, it was found that the proportion of diabetics among established PTB cases with no previous history of diabetes, was as high as 40%.[6]

There is consistent evidence from a number of studies, with different designs and from geographically diverse areas that diabetes is associated with an increased risk of TB,with an overall increased risk around 1.5 to 8.0 times higher.[1]

In the review of Sen et al., they suggested that diabetes may be diagnosed for the first time when blood sugars are initially sent off in the patient with PTB and found to be high. The authors advocate checking fasting and post-prandial sugars in all newly diagnosed TB patients.[7]

Biological basis of causality

The dominant manifestation of DM, namely hyperglycemia, has been assumed to favor the growth, viability and propagation of tubercle bacilli. Furthermore, it was thought that the concomitant increase in dextrose in the tissues resulted in decreased resistance to infection in situ and also in impaired repair capacity. Predilection to infection was also attributed to local tissue acidosis and imbalance of electrolytes.

In has also been postulated that pituitary gland dysfunction may have a role in the increased susceptibility to TB. A relative and absolute overproduction of adrenocorticotrophic hormone and consequent increased level of corticosteroids in the blood may interfere with the normal defense mechanism of the mesenchymal tissues. Moreover, as corticosteroids are insulin antagonists, their overproduction may result in insulin resistant DM.

Numerous studies have presented convincing biological evidence supporting impaired host immunity to TB due to DM. In experimental studies of human plasma cells, high levels of insulin have been shown to promote a decrease in Th1 immunity. Interferon gamma levels were also found to be significantly reduced in people with DM compared to controls without DM. The decrease in Th1 immunity and IFN gamma connotes impaired host immunity hence the propensity of patients with DM to have TB (as postulated).

Screening for Diabetes Mellitus in Tuberculosis

For patients with TB, previous studies suggest that it is more reliable to screen for DM later in the course of anti-TB treatment rather than at the start, because TB as a chronic infectious disease may elevate blood glucose levels because of cytokine stimulation resulting in false positive DM diagnosis if the investigation is performed too early. However, delayed screening may be a missed opportunity

for subsequently modifying treatment, and many TB programmes, especially in Africa, have decentralized services to peripheral facilities where it is difficult to get laboratory investigations performed.

Research is required to determine the optimal time and best methods for diagnosing DM in patients with TB, focusing on adults stratified by type of disease (smear-positive PTB, smear-negative PTB and extra-pulmonary TB). The most appropriate ways of screening should be explored (urine, random or fasting blood glucose and / or glycated haemoglobin A1c (HbA1c)).

Patients identified by the two screening strategies discussed earlier need to be entered into prospective studies assessing the impact of DM or non-DM hyperglycemia on TB treatment outcomes, using standardized TB regimens and outcomes, in which other confounding factors (age, smoking status, alcohol, body mass index and HIV) are taken into account. The level of hyperglycaemia and quality of diabetes control, measured, for example by HbA1c, are important factors to consider.

Primary treatment outcomes should include (i) liver function tests; (ii) pharmacokinetic levels of rifampicin and oral diabetes medications; (iii) TB treatment outcomes; (iv) recurrence of TB, one year after completion of TB treatment as determined by sputum culture; and (v) culture and drug sensitivitytesting, at the start of treatment and at the time of failure or TB recurrence to assess linkages and associations with drug-resistant TB.

Death is reported to be more frequent in patients with DM on anti-TB treatment, but research is required to address unanswered questions such as when death occurs in relation to start of anti-TB treatment, the aetiology, and whether better DM control or modified TB drug regimens, duration of anti-TB therapy and TB drug doses reduce case fatality.[1]

Materials and Methods

Study Design

Prospective Observational Cohort Study

Study Setting

Quezon Institute Philippine Tuberculosis Society, Inc. (PTSI) TB DOTS Center The study was reviewed and approved by the PTSI Technical Review Board and Ethics Committee.

Study Population

IInclusion Criteria:

All adult patients diagnosed with PTB, enrolled in the DOTS Program of Quezon Institute, receiving anti-TB treatment regardless of sputum-smear status, seen on an out-patient basis from July 2011-November 2012.

Exclusion Criteria:

1. Those who do not give consent for inclusion in the study.
2. Pregnant patients
3. Patients who are not legally competent.

Procedure

An informed consent was obtained prior to initiation of any study-related procedure. Patients with PTB who gave consent for enrolment in the study were screened for DM. Patients were identified using predetermined case numbers (assigned by the institution). A diabetes screening tool (Appendix 1) consisting of the age, presence of symptoms, risk factors including family history and past medical history related to or associated with DM were asked by the clinic nurse. The diagnosis of DM was done based on the criteria of either: 1) presence of symptoms and FBS > 126 mg/dL on one determination, 2) elevated HBA1c (>6.5) and 3) elevated FBS > 126 mg/dL on two separate occasions. The FBS was not repeated if the patient already fulfilled criteria #1 and #2 with one determination. If another test was needed, then a repeat FBS was done to fulfill criteria #3.

All patients were followed up prospectively during the course of TB treatment. The study ended when all patients included finished their DOTS treatment.

Statistical Method

Descriptive analysis was used for the characterization of PTB in patients with DM compared to those who had no DM. The prevalence of diabetes among people with PTB was estimated by calculating the number of PTB cases in the populations with and without DM, and hence the percentage of cases with DM, with the corresponding 95% confidence interval. Fisher's exact test was used to determine the p-values to compare variables in patients with and without DM with 95% confidence interval. Logistic regression analysis was used to test for differences between TB patients with and without DM. Stata version 11.0 was used for the analysis.

Results

Thirty-eight patients diagnosed with PTB and enrolled in PTSI TB DOTS were recruited in this study. These were the patients who were screened to be eligible for enrollment and who gave consent for inclusion in the study. Fourteen of these patients were referred to PTSI by a satellite TB DOTS center. Out of the 38, seven (18.4%, 95% confidence interval 7.7-34.3) were diagnosed with DM.

The demographic data of the 38 patients included in the study are shown in Table I.

Study Flow Chart

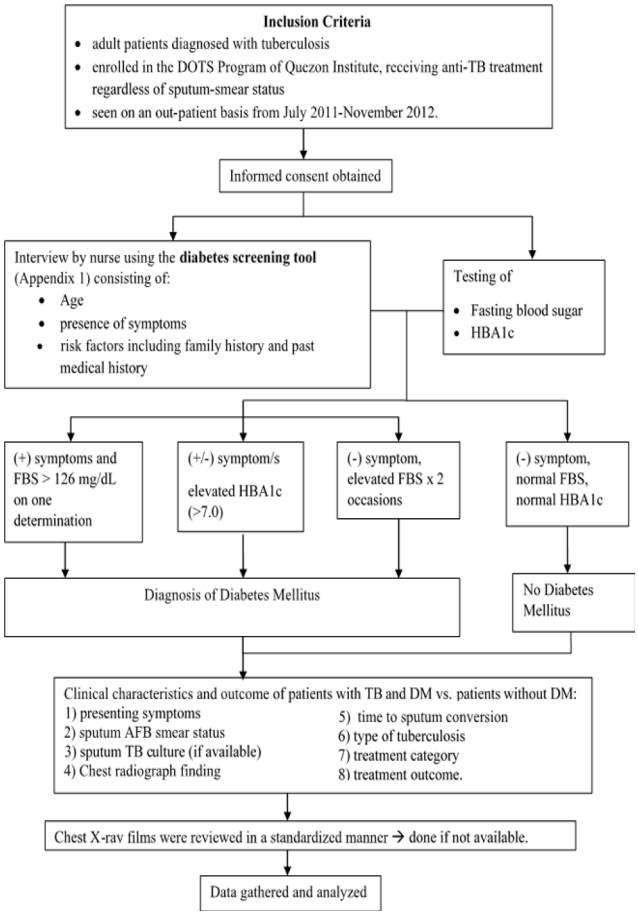

Table I: **Demographic profile of patients with and without DM diagnosed with PTB.**

	No. of patients		
	DM N=7 (%)	No DM N=31 (%)	Total N=38 (%)
Sex			
Male	4 (57)	22 (71)	26 (68.4)
Female	3 (43)	9 (29)	12 (31.5)
Age			
Mean	42.83	43.31	43.24
SD	16.67	17.32	16.77

The clinical and radiographical presentation of PTB with and without DM are shown in Table II. The most common symptom of patients for both groups was cough, followed by weight loss and fever. Dyspnea was more frequent among patients with DM. However, there was no statistically significant difference among all the symptoms for both patients with and without DM patients occurring more in patients with DM.

As for the radiographic findings (also shown in Table II), there was noted to be more occurrence of lower lobe and bilateral CXR findings among patients with DM. Most of the infiltrates were described to be reticular, reticulonodular or reticulolinear for both patients with and without DM. Cavitary lesions on CXR were more commonly seen in patients with DM but the difference was not statistically significant .

Table II: **Clinical and radiographic presentation of TB in patients with DM.**

	No. of patients n(%)		
	DM N=7	No DM N=31	p-value*
TB symptoms			
Fever	3 (42.8)	15 (48.3)	0.563
Cough	7 (100.0)	28 (90.3)	0.533
Weight loss	6 (85.7)	27 (87.1)	0.661
Malaise	3 (42.8)	11 (35.5)	0.517
Hemoptysis	3 (42.8)	6 (19.4)	0.199
Chest pain	4 (57.1)	10 (32.2)	0.210
Dyspnea	5 (71.4)	10 (32.2)	0.070
CXR findings			
Upper	0 (0)	5 (16.1)	0.373
Lower	0 (0)	11 (35.5)	0.082
Bilateral infiltrates	2 (2.8)	7 (22.6)	0.479
Cavity	2 (28.5)	7 (22.6)	1.000

*Fisher's exact test

The next table compares sputum conversion for patients with DM and those without DM. Based on the results, there is a statistically significant number of sputum smear positive patients for those with DM compared to those without DM. There were also more patients with negative sputum smears among patients without DM. As for the sputum conversion, all of the sputum AFB smear positive patients with DM converted to negative after two months and remained as such after five months of treatment. There was no finding of delayed sputum conversion. On the other hand, sputum conversion for patients without DM was 83% after two months but was 100% after five months of treatment. Based on Table IV, the risk of having positive sputum among patients with DM is 9.5 times than patients without DM .

Since all of the patients who initially had positive sputum converted to negative after intensive phase of treatment, these patients' treatment outcomes were determined to be cured. This is true for both patients with and without DM who had initially positive sputum AFB smears. The rest of the patients completed the treatment. There were no defaulters nor there was any fatality noted.

Table III: **Sputum conversion of patients with and without DM diagnosed with PTB**

		No. of patients n(%)		
		DM N=7	No DM N=31	p-value
Intial sputum				
	Positive	6 (85.7%)	12 (38.7%)	
	Negative	1 (14.3%)	19 (61.3%)	0.038
		7	31	
After two months				
	Positive	0 (0%)	2 (6.4%)	
	Negative	6 (100%))	29 (93.6%)	1.000
		6	31	
After 5 months				
	Positive	0	0	Cannot compute
	Negative	6 (100%)	29 (100%)	Cannot compute

Table IV demonstrates the association of some of the different clinical and radiographic variables with the occurrence of DM. The odds ratio for the risk of having DM with the presence of the corresponding variable among patients with TB were determined. For instance, male patients with PTB have 0.545 times risk of having DM (thus lesser risk of having DM). Of all the symptoms elicited, dyspnea and hemoptysis portend the higher risk of occurrence among PTB patients with DM (OR 5.25 and 3.12, respectively). However, among these and the rest of the variables, none were shown to be of significant risk.

Table IV: **Association of factors with DM using univariate logistic regression**

	No. of patients (N=38)		
	DM N=7	No DM N=31	Odds ratio (95% CI)
Sex			
Male	4	22	0.545 (0.101, 2.944)
Female	3	9	
Age			
Mean	48.86	13.33	0.980 (0.940, 1.021)
SD	5.04	17.66	
Fever			
Yes	3	15	0.312 (0.074, 1.315)
No	4	16	
Weightloss			
Yes	6	27	0.889 (0.084, 9.443)
No	1	4	
Malaise			
Yes	3	11	1.364 (0.257, 7.229)
No	4	20	
Hemoptysis			
Yes	3	6	3.125 (0.547, 17.841)
No	4	25	
Chestpain			
Yes	4	10	2.800 (0.524, 14.959)
No	3	21	
Dyspnea			
Yes	5	10	5.25 (0.864, 31.901)
No	2	21	
Initial Sputum AFB positive			
Yes	6	12	9.5 (0.92, 459.33)
No	1	19	
Bilateral infiltrates			
Yes	2	7	1.71 (0.234, 12.551)
No	3	18	
Cavity			
Yes	2	7	1.37 (0.11, 10.90)
No	5	31	

Discussion

In this study, the prevalence estimate of DM among patients with TB is 18.4%. However, since the confidence interval of this prevalence estimate is too wide, its accuracy may not be very reliable because of the small sample size. In the WHO report in 2009 where the Philippines is ranked ninth among top 10 countries with TB, 12.9% of TB cases are attributable to DM in 2010 while it is estimated to rise to 14.4% in 2030.[12] In the study of Li et al., in China in 2012, the overall prevalence of DM in patients in TB was 12.4%[10] while in the study by Kumar et al., in India in 2012, the prevalence rate was 13%.[11] Other studies from various parts of the world in the past decade showed a wide range of results with DM present concomitantly in 5.0-30% of patients with TB.[12] Although it is possible that the actual prevalence of DM among TB patients is higher than previous estimates, the true prevalence of DM among patients with PTB in our country would still be better known by doing a large multicenter cohort or cross-sectional study as was done in China and India. Both of these studies included more than 8,000 patients. It must be noted that parameters used to diagnose DM may be different. Both studies used FBS ¬> 126 mg/dl (equivalent to > 7.0 mm in China) as cut-off value for screening for presumptive DM. Those patients with possible DM were referred to their respective DM clinics for definitive diagnosis. It was not described in detail, however, what criteria were used to make a definitive diagnosis in their DM clinics.[10,11]

In the determination of the true prevalence of DM, several factors should be taken into consideration. One is that some patients diagnosed with DM may actually be having non-diabetic stress hyperglycemia which may occur in association with an infection.

Thus, interpretation of glucose parameters should be taken with precaution and may be better confirmed after elimination of the infection.[13] Another consideration is the capacity of the health system to diagnose DM at an early stage since DM is said to be a time-dependent risk factor for TB.[12] It may also be useful to determine if the DM is Type 1 or Type 2 since although Type 1 is more prevalent, type 1 DM is said to be associated with a higher risk of TB.[12]

There was almost equal prevalence of DM among both sexes which is consistent with published studies finding no gender difference between diabetic and non-diabetic patients.[12] The mean age of patients for both DM and non DM patients were almost the same as well and mostly were over the age of 40, and this was consistent with most previous studies.[8,9,10,11]

The symptoms experienced by the patients with DM in this study did not significantly differ from those without DM. This was consistent with the study of Bacakog et al., in 2001.[7] A more recent study in Tanzania involving 1250 patients also concluded that DM is associated with small changes in the manifestations of TB, but may be of little clinical significance in terms of disease-related symptoms.[13] Based on many published studies, there is uncertainty as to whether DM affects the clinical presentation of TB and this is attributed to differences in patient selection and case definition of DM.[12] In particular, the occurrence of weight loss and fever, which were observed by some clinicians in to be more protracted in patients with DM, were almost of the same rates among patients with and without DM in this study.

The radiographic findings of patients with DM likewise did not significantly differ from those without DM. For instance, the occurrence of cavity which was purported to be more prevalent in patients with DM was almost of the same rate as in those without DM in this study. Previous studies have also found correlation of occurrence of lower lobe infiltrates in patients with DM[8] but this was not observed in our patients. In fact, none of the patients with DM had CXR findings affecting the lower lung field. Available literature determining radiological appearance of TB actually had conflicting results.[12]

The number of patients with DM having positive sputum AFB smears are significantly more than the number of patients without DM. Some previous studies are consistent with this finding[14,15,16] but other studies showed otherwise.[7,8] However, the sputum conversion after intensive phase of treatment was similar for both groups. This is in contrast with other studies showing longer sputum smear conversion for patients with DM.[8]

The treatment outcomes and survival of PTB patients with and without DM were similar. This is consistent with more recent studies showing that the survival rate of adequately treated patients with DM and PTB are the same as that of TB patients without DM.

The study's main limitation was that the number of recruited patients were small (30% of all patients enrolled in PTSI TB DOTS from June 2011-November 2012). The main reason behind poor recruitment was the lack of consent for procedures since the patients had to go back for tests (FBS was fasting) and travel costs were at their own expense. The additional effort and expense in screening for DM may account for the non-participation of some patients. This could have been circumvented by allotment of funds for their transportation allowance. However, we did try to augment recruitment by engaging nearby health centers and having them refer potential patients to the PTSI TB DOTS for screening.

We conducted one-on-one meetings with recruited patients to explain the results of the laboratory tests and those diagnosed with DM were referred to the DM clinic for further management. Although it may be difficult to establish occurrence of actual DM against stress-induced hyperglycemia while the patient has active TB, it is still be worthwhile to conduct lifestyle counselling and health promotion since these may prevent or delay onset of DM.[10] The use of HBA1c (as in this study) or a two-hour oral glucose tolerance as a screening tool may be more reliable in diagnosing true DM although more studies should be done to establish this.

It is a reality that our country has a high burden of TB and while DM is of increasing burden worldwide, our goal of eradicating TB will definitely be more challenging. This study demonstrated that screening for DM among patients with TB is feasible. But larger studies should be done to produce more conclusive evidence of how DM affects the manifestations and outcomes of patients being treated for TB. It would be very beneficial if we can come up with a screening algorithm that can be standardized and used appropriately in our local setting. Further studies may also analyze the cost-effectiveness of such screening procedures. Other aspects of the implications of DM on TB that warrant further investigation would include interactions of DM medications with anti-TB drugs, resistance rates, and extrapulmonary tuberculosis among patients with DM.

It has already been recommended by the World Health Organization and the International Union Against Tuberculosis and Lung Disease in

their Collaborative Framework for Care and Control of Tuberculosis and Diabetes in 2011 that patients with TB should be screened for DM at the start of treatment and that the type of screening be adapted to the context of local health systems and availability of resources, while awaiting additional evidence on best screening and diagnostic approach. Furthermore, management of DM should be provided in line with existing guidelines.[17]

Conclusion

In this study, the prevalence of DM among patients with TB was 18.4% which was higher than the prevalence noted in other studies. There was no significant difference noted on the basic profile, clinical and radiographic presentation and sputum conversion among patients with DM and without DM who are being treated for PTB. There is still uncertainty as to whether DM affects clinical presentation of TB as more studies showed that there is no significant association as shown in this study. Although this study demonstrates the feasibility of screening for DM among patients with PTB, a multi-center study with a larger sample size must be conducted to more accurately measure the true prevalence of DM among patients with PTB and its implications on PTB treatment and outcomes.

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Appendix 1

DATA COLLECTION TOOL

Initials:_____
Patient Number:_____
Presenting symptoms:

☐ fever ☐ cough ☐ weight loss ☐ malaise

☐ hemoptysis ☐ chest pain ☐ dyspnea

☐ others

Sputum AFB Smear Status:

	Day 1	Day 2	Day 3
Baseline			
After 2 months			
After 5 months			

Sputum TB Culture: _____

Sensitive to: ☐ Isoniazid ☐ Rifampicin ☐ Pyrazinamide ☐ Ethambutol

Resistant to: ☐ Isoniazid ☐ Rifampicin ☐ Pyrazinamide ☐ Ethambutol

Chest Xray findings: date taken:_____

☐ upper lobe, R/L ☐ lower lobe, R/L

☐ cavitary lesion (location:_____)

☐ others:

☐ Pulmonary ☐ Extrapulmonary; site:_____

Type: ☐ New ☐ Relapse ☐ Treatment Failure

☐ Return to treatment after default ☐ Transfer-In ☐ Others:

Treatment Category: I II III

Treatment Outcome: ☐ Cured

☐ Completed (no sputum follow-up)

☐ Treatment Failure (still smear + at 5 months)

☐ Defaulter (interrupted for >2 months)

☐ Transfer Out (change in treatment facility)

☐ Died (dies during treatment)

DIABETES SCREENING TOOL

Initials: _____ Patient no.:_____ Age: ____ Sex: ☐M ☐F
Diagnosis: _____

Symptoms: ☐ polyuria :____x/day ☐ weight loss ☐ frothy urine

☐ polyphagia ☐ paresthesia ☐ pruritus

☐ polydyspsia ☐ blurring of vision ☐ edema

Past Medical history: ☐ Diabetes Mellitus: (year diagnosed:_____,meds:_____)
Diagnosed in: local health center /hospital

☐ Dyslipidemia: (year diagnosed:_____,meds:_____)

☐ Hypertension: (year diagnosed:_____,meds:_____)

☐ Stroke: (year diagnosed:_____,meds:_____)

☐ Heart Disease: (year diagnosed:_____,meds:_____)

Family Medical History of Diabetes: ☐ Parent ☐ Both parents ☐ grandparent/s
☐ Others:_____

Weight:_____kg Height:_____ cm BMI:_____kg/m2
Baseline FBS: _____
HBA1c:_____
Notes:
_____