A CROSS SECTIONAL SURVEY OF PULMONARY TUBERCULOSIS AMONG ELDERLY DIABETICS ATTENDING PRIMARY CARE CLINICS IN PENANG, MALAYSIA

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Abstract. Latent tuberculosis (TB) is more likely to convert to active TB with increasing age and with poorly controlled diabetes mellitus (DM). We aimed to determine the prevalence of and factors associated with pulmonary tuberculosis (PTB) among elderly patients with DM attending public primary care clinics in Penang, Malaysia in order to inform TB control efforts among elderly with DM. Study subjects were selected from 15 primary care clinics. A total of 4,209 subjects were calculated to be needed for the study assuming a PTB prevalence among elderly diabetics of 3.89 per 1,000 among the study population obtained from the National Diabetic Registry (NDR) of patients aged ≥ 60 years consisting of 22,980 patients. Study subjects were randomly selected from the NDR of patients aged ≥ 60 years. Inclusion criteria were being aged ≥ 60 years and having DM. The exclusion criteria was being treated for TB. A total of 4,209 subjects were included in the study. Each subject was interviewed and asked about PTB symptoms defined as cough > 2 weeks, weight loss, night sweats or fever > 4 weeks and other past medical problems. Each subject had a chest x-ray (CXR) and blood test for serum creatinine and glycated hemoglobin (HbA1c). Subjects with a cough were asked to give a sputum sample for acid-fast bacilli (AFB) stain. Subjects were classified as either having sputum smear positive PTB, sputum smear negative PTB or not having PTB. Criteria used to classify a subject as having sputum smear positive PTB were having a sputum smear positive for AFB and having an abnormal chest radiograph (CXR) with findings typical of active PTB. Sputum smear negative

PTB was defined as having a sputum smear negative for AFB, having symptoms of PTB and having an abnormal CXR with findings typical of active PTB. Sputum smear positive PTB and smear negative PTB were grouped as having PTB in this study. The socio-demographic and clinical factors associated with PTB were determined using logistic regression analysis. A total of 4,209 subjects were included in the study. The mean (± standard deviation) age of study subject was 68.8 (±6.4) years. Eight out of 4,209 subjects (0.19%) were diagnosed with having PTB; 6 (0.14%) were classified as having smear positive PTB and 2 (0.05%) as having smear negative PTB. This gives a PTB prevalence of 1.9 per 1,000 population. This is far lower than the 3.9 per 1,000 prevalence used to calculate the number needed for the study. The mean HbA1c among subjects with PTB was significantly higher than among subjects without PTB (OR=1.3; 95% CI: 1.01-1.76; p=0.040). There were no other factors significantly associated with having PTB. Diabetic patients aged ≥60 years with an elevated HbA1c having symptoms of PTB in the study population should be screened for PTB.

Keywords: pulmonary tuberculosis, elderly diabetes mellitus, screening, HbA1c

INTRODUCTION

Tuberculosis (TB) and diabetes mellitus (DM) are public health problems (Lin *et al*, 2015). In 2016, the World Health Organization (WHO) estimated 10.4 million people were infected with TB worldwide and 1.67 million died (WHO, 2017). Malaysia had an intermediate incidence of TB of 92 per 100,000 in 2015 (WHO, 2017). The International Diabetes Federation (IDF) 2015 report states 415 million people worldwide have DM, of which 153 million people were from the West Pacific Region. It is estimated that by 2040 this will rise to 642 million. In Malaysia, there were 3.3 million cases of diabetes in 2015 (IDF, 2015).

Many factors are associated with reactivation of TB, such as an impaired immune system (host factor) and exposure to infectious persons (environmental factors). Diabetic patients (Nissapatorn *et al*, 2006; Reis- Santos *et al*, 2013; Sulaiman *et al*, 2013; Lin *et al*, 2015), patients with renal disease (Hussein *et al*, 2003), elderly patients (Workneh *et al*, 2017), smokers (Kumpatla *et al*, 2013; Lin *et al*, 2015) and underweight patients (Kumpatla *et al*, 2013) are at higher risk for TB reactivation. Household contacts (Lin *et al*, 2015), birth in a TB-endemic areas and crowded community settings (Stead *et al*, 1985; Maclntyre *et al*, 1997) are environmental factors associated with TB reactivation.

Many studies have looked at the relationship between TB and DM. In Malaysia, there was a steady decrease in the incidence of TB between 1990 and 2012 from 127 per 100,000 in 1990 to 80 per 100,000 in 2012 (Ghazali, 2014). However, in Malaysia there has been an increase in the prevalence of non-communicable diseases, such as DM. Based on the National Health Morbidity Survey (NHMS) in 2015, the prevalence of DM increased from 11.6% in 2006 to 17.5% in 2015. (Institute for Public Health, 2015). A higher prevalence of DM may be associated with

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a higher incidence of TB. The risk for developing TB among diabetics is three times higher than those without DM (Jeon and Murray, 2008). A study from Penang, Malaysia reported one-third of patients diagnosed with pulmonary TB (PTB) had DM (Elamin *et al*, 2004). Diabetes may also complicate the care, control and outcomes of TB (WHO, 2011; Reis- Santos *et al*, 2013; Lin *et al*, 2015).

The World Health Organization and others have recommended screening for TB among diabetic patients (WHO, 2011; Ghazali, 2014; Lin *et al*, 2015). In Penang, state health department guidelines recommend all diabetic patients aged ≥ 60 years should be screened once for PTB with a chest x-ray (CXR) (Penang Health Department, 2014) followed by yearly symptomatic screening.

This study aimed to determine the prevalence of and factors associated with PTB among diabetics aged ≥ 60 years in Penang, Malaysia in order to inform and guide TB screening among elderly diabetics in the study population.

MATERIALS AND METHODS

Study design and setting

We conducted a multi-center analytical cross-sectional study of subjects attending 15 public primary care family medicine clinics in Penang, Malaysia.

Study size

The study population size was based on the estimated prevalence of TB among elderly diabetic patients of 3.89 per 1,000 population reported in Taiwan (Lin *et al*, 2015), with a 95% confidence interval (CI) and 5% precision; the sample size required was determined to be 3,788; adding 10% for non-response, the total study population needed was determined to be 4,209 subjects.

Sampling method

In Penang, at the time of the study there were 22,980 patients aged ≥ 60 years registered in the National Diabetes Registry. This was the patient population we selected our study subjects from. The number of subjects chosen from each of the 15 study clinics was based on the prevalence of DM patients at the clinic. The subjects were chosen randomly from the patient population using EpiCalc 2000, version 1.0 (Brixton Health). Study subjects were recruited during 1 February 2016 - 31 October 2016 when they presented for their regularly scheduled appointment for their DM. Subjects who were too ill or who were on TB treatment were excluded from this study. For those who refused to participate in the study, further random sampling was used to choose other subjects until the required number of subjects was achieved.

Study instrument

Each subject was asked to complete a questionnaire consisting of 26 items in 6 sections, pilot tested on 30 subjects at one of the study clinics. Modification of the pilot tested questionnaire was made based on the feedback obtained.

Section 1 of the questionnaire asked about demographics and other variables: age, gender, ethnicity, height, weight, occupation, education level, smoking status, history of previous TB infection and history of TB contacts.

Section 2 asked about other factors related to PTB: history of HIV, end-stage renal disease, malignancy and type or long term corticosteroid use and its indications.

Section 3 asked about PTB symptoms and their duration: history of cough, night sweats, fever or weight loss. Criteria considered positive for PTB symptoms in this

study were: cough for > 2 weeks, weight loss, night sweats or fever for >4 weeks (Ghazali, 2014).

Section 4 recorded the results of serum creatinine and glycated hemoglobin A1c (HbA1c) and CXR results.

Section 5 recorded further management based on symptom screening and CXR results: referral to a radiologist for CXR reporting, referral to a chest physician, examination of sputum for acid-fast bacilli (AFB) stain or treatment with antibiotics or an expectorant for subjects suspected of not having PTB.

Section 6 recorded the outcomes of section 5: sputum AFB stain results, results of sputum culture for *Mycobacterium tuberculosis* (MTB), CXR results per radiologist and results of chest physician consultation. The final diagnosis was also recorded in section 6.

Data collection

The physicians and nurses at the study clinics were briefed on the objectives of the study, the screening process, flow and data collection process.

The study blood test results were obtained from the study subject chart if performed within the previous 6 months or were ordered. Serum creatinine was used to indicate renal impairment. Patients with renal failure have been reported to have a higher risk in reactivation of PTB (Hussein *et al*, 2003). The CXR results from the study subject were obtained from the chart if performed within the previous year or a CXR was ordered. The CXRs were interpreted by the treating doctors. Abnormal or inconclusive CXR films were sent to a radiologist for reading.

Diagnosis of pulmonary tuberculosis

Three sputum samples for AFB stain were obtained from each subject who presented with cough. Sputum smear positive PTB was defined as having at least one sputum sample positive for AFB, a CXR result consistent with typical PTB (consolidation/cavitations of an upper lung zone) and/or having symptoms of PTB (cough for > 2 weeks, weight loss, night sweats or fever for >4 weeks). Subjects with sputum smear negative for AFB or having other symptoms of PTB with an abnormal CXR with typical findings of active PTB were referred to a chest physician to exclude smear negative PTB. Chest physicians evaluated the subjects with either a CT scan of the thorax and/or bronchoscopy with washings for AFB. Subjects were then classified as being either sputum smear positive or smear negative PTB.

Data analysis

The Statistical Package for Social Sciences, version 21(IBM, Armonk, NY) was used to carry out statistical analyses. Of the 4,209 subjects, 76 had missing data: height, weight, serum creatinine or serum HbA1c levels. These subjects were excluded from the analyses of their respective missing variables.

Descriptive statistics were used to describe the socio-demographic characteristics of the study subjects. Continuous variables were described by means ± standard deviations (SD) or medians + interquartile ranges (IQR) while categorical variables were described by percentages.

Logistic regression analysis was used to evaluate potential associations between PTB and independent factors. Some of these factors were re-categorized to facilitate statistical analysis. Race was categorized as either Chinese or non-Chinese (Malay, Indian, others). Body mass index (BMI) was categorized as either normal (18.5-22.9 kg/m^2) or

abnormal (<18.5 kg/m^2 or ≥ 23 kg/m^2) (Ministry of Health Malaysia, 2004). Occupation was categorised as working or not working. Those who were retired were categorized as not working. Education level was defined as lower (no or primary school education) or higher (greater than primary school education). Smoking was categorized as smokers (current smokers) or non-smokers (ex-smokers or never smoked). A p-value < 0.05 was considered statistically significant.

Ethical approval

This study was approved by the Medical Research Ethics Committee, National Medical Research Registry, Ministry of Health, Malaysia (NMRR-15-1691-27163). Verbal informed consent was obtained from each subject and documented in their medical record prior to being included in the study.

RESULTS

A total of 4,209 subjects were included in the study. Of these, 4,133 (98.2%) had no missing data. Table 1 summarizes the socio-demographic characteristics of the subjects. Fifty-seven point three percent of subjects were females and 45.7% were of Chinese ethnicity. The mean (±SD) age of study subjects was 68.81 (±6.42) years. Eighty-five subjects (2.0%) had a previous history of TB. The mean (±SD) HbA1c level was 7.7 (± 1.9) %.

Table 1
Characteristics of 4,209 study subjects.

	n (%)
Mean (±SD) age in years	68.8 ± 6.4
Gender	
Male	1798 (42.7)
Female	2411 (57.3)
Ethnicity	
Malay	1625 (38.6)
Chinese	1924 (45.7)
Indian	647 (15.4)
Others	13 (0.3)
Mean BMI ±SD in kg/m^2	26.1 ± 4.6
< 18.5	112 (2.7)
18.5-22.9	900 (22.1)
23-27.4	1733 (42.5)
≥27.5	1335 (32.7)
Residentce	
Home	4180 (99.3)
Nursing home	29 (0.7)
Education level	
Primary	1947 (46.3)
Secondary	1662 (39.5)
Tertiary	170 (4.0)
No schooling	430 (10.2)
Occupation	
Working	474 (11.3)
Retired	1255 (29.8)
Not working	2480 (58.9)
Smoking status	
Smoker	334 (7.9)
Non-smoker	3472 (82.5)
Ex-smoker	403 (9.6)
Previous TB infection	
Yes	85 (2.0)
No	4124 (98.0)
History of TB contact	
Yes	76 (1.8)
No	4133 (98.2)
ESRD	
Yes	24 (0.6)
No	4185 (99.4)
Malignancy	
Yes	41 (1.0)
No	4168 (99.0)
Mean HbA1c (± SD) in %	7.7 ± 1.9
Median (IQR) serum creatinine level in μmol/dl	92 (41)

SD, standard deviation; BMI, body mass index; TB, tuberculosis; ESRD, end-stage renal disease; IQR, inter-quartile range.

Table 2
Characteristics of study subjects by PTB status.

	PTB (n=8) n (%)	No PTB (n= 4,201) n (%)	OR	95%CI	p-value
Mean (±SD) age in years	69.5 ± 8.1	68.8 ± 6.4	0.98	0.89-1.09	0.762
Gender					
Male	5 (62.5)	1798 (42.7)	0.45	0.11-1.87	0.270
Female	3 (37.5)	2408 (57.3)	1.00		
Ethnicity					
Chinese	2 (25.0)	1922 (45.8)	2.23	0.51-12.55	0.256
Non-Chinese	6 (75.0)	2279 (54.2)	1.00		
Mean BMI ±SD in kg/m^2	26.6 ± 5.8	26.1 ± 4.6	0.98	0.84-1.13	0.731
Normal	3 (37.5)	925 (22.0)	2.13	0.51-8.91	0.303
Abnormal	5 (62.5)	3276 (78.0)	1.00		
Residentce					
Home	8 (100.0)	4172 (99.3)	*	*	> 0.950
Nursing home	0 (0.00)	29 (0.7)			
Education level					
Lower	6 (75.0)	2371 (56.4)	0.43	0.09-2.14	0.304
Higher	2 (25.0)	1830 (43.6)	1.00		
Occupation					
Working	1 (12.5)	473 (11.3)	0.89	0.11-7.23	0.912
Not working	7 (87.5)	3728 (88.7)	1.00		
Smoking status					
Smoker	1 (12.5)	333 (7.9)	0.60	0.07-4.91	0.636
Non-smoker	7 (87.5)	3868 (92.1)	1.00		
Previous TB infection					
Yes	0 (0.0)	85 (2.0)	*	*	> 0.950
No	8 (100.0)	4116 (98.0)			
History of TB contact					
Yes	1 (12.5)	75 (1.8)	0.13	0.02-1.05	0.055
No	7 (87.5)	4126 (98.2)	1.00		
ESRD					
Yes	0 (0.0)	26 (0.6)	[a]	[a]	> 0.950
No	8 (100.0)	4175 (99.4)			
Malignancy					
Yes	0 (0.0)	41 (1.0)	[a]	[a]	> 0.950
No	7 (100.0)	4161 (99.0)			
Mean HbA1c (± SD)	9.1 ± 2.2	7.7 ± 1.9	1.30	1.01-1.76	0.040[b]
Median (IQR) serum creatinine level in μmol/dl	102 (64)	92 (41)	1.00	1.00-1.01	0.312

SD, standard deviation; BMI, body mass index; TB, tuberculosis; ESRD, end-stage renal disease; IQR, interquartile range; [a] cannot be generated due to insufficient data; [b] $p< 0.05$.

PTB, pulmonary tuberculusis; OR, odds ratio; CI, confidence interval.

Table 2 shows the association between selected variables and PTB status. Of the 4,209 study subjects, 6 were classified as having sputum smear positive PTB and 2 as having sputum smear negative PTB. This gives a PTB prevalence of 1.9 per 1,000 population (8/4,209). These 2 groups were combined together into the PTB group in Table 2.

For every percent increase in the HbA1c, the odds of having PTB increased by 1.3 times. (Odds ratio=1.30; 95% Confidence interval: 1.01-1.76; $p = 0.040$). No other variables in Table 2 were significantly associated with PTB.

Table 3 summarizes the symptoms of the 8 subjects classified as having PTB. Eighty-seven point five percent of the PTB subjects had at least one symptom but none had weight loss.

Table 3
Summary of symptoms among subjects with PTB.

Symptoms	Subjects *n* (%)
Cough	
Yes	7 (87.5)
No	1 (12.5)
Loss of weight	
Yes	0 (0.0)
No	8 (100.0)
Night sweats	
Yes	1 (12.5)
No	7 (87.5)
Fever	
Yes	1 (12.5)
No	7 (87.5)
Presence of symptoms	
Yes	7 (87.5)
No	1 (12.5)

DISCUSSION

In this study, the prevalence of PTB among our elderly diabetic study subjects was 1.9 per 1,000. This prevalence is similar to a study from Bangladesh (2.13 per 1,000) (Rahim *et al*, 2012), but lower than a study from Taiwan (3.89 per 1,000) and much lower than a study reviewing PTB in Asia (0.38-14%) (Workneh *et al*, 2017). The prevalence of PTB in our study may have been lower due to our exclusion of PTB patients undergoing TB treatment and our focus only on elderly diabetics.

In our study, a higher HbA1c level was associated with PTB, similar to other studies (Leung *et al*, 2008; Webb *et al*, 2009; Ahmed *et al*, 2017; Zheng *et al*, 2017). Restrepo *et al* (2008) reported persistent hyperglycemia can alter the immune responses to *Mycobacterium tuberculosis* among diabetic patients. Patients with poorer control of their DM may have an altered innate and cellular cytokine response (Restrepo *et al*, 2008) and lower interferon-gamma (IFN-γ) production (Tsukaguchi *et al*, 1997) enabling progression to active TB. However, only eight subjects were diagnosed with PTB in our study, so our results need to be interpreted cautiously.

Of the 8 patients in our study diagnosed with having PTB, only one did not have typical PTB symptoms; that patient reported only cough three days duration. These findings suggest symptoms of PTB may be a screening tool to determine which patients should have a screeing CXR. A WHO report stated a large proportion of TB cases are clinically diagnosed (WHO, 2017).

Our study had several strengths: it was a multi-center study involving a large number of subjects, conducted in clinics

in urban and semi-urban areas in Penang State. Simple random sampling with proportionate allocation was used to provide a good representation of the clinic attendees. The results should be applicable to all elderly diabetics in Penang State.

Our study also had some limitations. First, the CXRs were interpreted by the treating doctors; den Boon *et al* (2006) recommended with TB prevalence studies, CXRs should be read by an independent person to reduce inter-reader variability and bias. However, all the clinics involved in this study had undergone regular X-ray reading quality audits twice yearly. Second, the number of variables associated with reactivation of PTB in our study was fewer than other studies (Lin *et al*, 2015; Workneh *et al*, 2017). Other studies have reported associations between renal disease, smoking and abnormal BMI with PTB (Hussein *et al*, 2003, Kumpatla *et al*, 2013; Lin *et al*, 2015; Workneh *et al*, 2017).

We did not find any of these associations, possible due to the low prevalence of PTB in our study. An elevated HbA1c in our study was significantly associated with the reactivation of PTB suggesting elderly diabetics in Penang State should be monitored for signs and symptoms of PTB and possible further screened for PTB. Further studies are needed to determine if screening such patients can significantly improve the detection rates for reactivation of PTB.

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DECLARATION OF CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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