TUBERCULOSIS IN DIABETIC PATIENTS: A CLINICAL PERSPECTIVE

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Abstract. This retrospective and descriptive study was a report on the clinical situation of tuberculosis in diabetic patients, with 1,651 patients recruited. The mean age of TBDM patients was significantly higher than that of non-diabetic patients ($p<0.05$). Moreover, TBDM patients had a higher ratio of male to female than the other group. The significant proportion of TB appeared to increase steadily with age in diabetic patients compared to non-diabetic ones ($p<0.05$). However, they showed similarities in terms of sex, race, marital status, present address, and occupation. A higher percentage of pulmonary tuberculosis (91.4%) was shown in the TBDM group. We found that both groups had no differences in the radiological findings, with opacity or cavity of the upper lobe involvement being 89% and 91% in TBDM and non-diabetic groups, respectively. TBDM patients were shown to have more treatment success (33.3%), particularly the pulmonary type of tuberculosis in the longer duration (≥ 9 months). Further findings demonstrated that a lower proportion of the TBDM group defaulted in their treatment (19.8%) and experienced resistance to anti-tubercular therapy (1.4%) compared to non-diabetics.

INTRODUCTION

Tuberculosis continues to be a major threat to the health of the world, with an estimated 8-10 million new cases and 3 million deaths annually (Kochi, 2001). The global resurgence of TB has been accompanied by an increased frequency of multi-drug resistant *Mycobacterium tuberculosis* (MDR/TB) (Frieden *et al*, 1993; Pablos-Mendez *et al*, 1998). In Malaysia, it has been reported that tuberculosis is among the top 5 communicable diseases, and the trend of tuberculosis notification rates has been constantly increasing from 60/100,000 population in the year 1991 to 66/100,000 in the end of year 2001 (Ministry of Health Malaysia, 2003). Every year there has been an increase of 670,000 Malaysian people afflicted with diabetes mellitus, from 1.4 million in 1998 to 1.8 million in 2002 (Ministry of Health Malaysia, 2002). Tuberculosis continues to be a disease of great impact in Malaysia but there is no data known on TB in diabetic patients. We therefore conducted this study in order to compare epidemiology and clinical impacts of tuberculosis between diabetic (TBDM group) and non-diabetic (TB group). These findings provided significant evidence and contributed to a better understanding and proper management in the course of tuberculosis among diabetic patients.

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MATERIALS AND METHODS

Patients

There were 1,651 non HIV-infected patients registered for tuberculosis treatment from January 2001 to December 2002 at the National Tuberculosis Center (NTBC), Kuala Lumpur, Malaysia. This center is a tertiary national reference center for respiratory diseases situated in Kuala Lumpur, Malaysia. Any person with a respiratory problem can attend this center without a physician referral and majority of notified TB cases in Kuala Lumpuur territory each year are treated there. Data were retrospectively reviewed from each patient's medical record. The following information was listed in the standardized data collection sheet: socio-demographic profiles, clinical presentation and investigation results, treatment, medications and duration, patient compliance with therapy, and outcome of therapy response. A total of 241 tuberculosis patients with diabetes (TBDM group) were included. Diabetes mellitus was confirmed by at least two-serum fasting glucose levels over 140 mg/dl. An additional group of 1,410 patients with only tuberculosis (TB group) were included and used as control. In the population studied, neither the TBDM nor the TB patients had clinical suspicion of human immunodeficiency virus (HIV) or acquired immune-deficiency syndrome (AIDS); HIV status was tested by various serological tests (ELISA (I,II), CLIA, or LA).

Definitions

Disease categories. The following definitions were recommended by the World Health Organization (2003):

Case of tuberculosis: a patient in whom tuberculosis has been bacteriologically confirmed, or who has been diagnosed by a clinician.

Pulmonary tuberculosis, sputum smear positive (PTB+): (1) two or more initial sputum smear examinations positive for Acid-Fast Bacilli (AFB) or (2) one sputum smear examination positive for AFB plus radiological abnormalities consistent with active pulmonary tuberculosis as determined by a clinician, or (3) one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis.*

Pulmonary tuberculosis, sputum smear negative (PTB-): a case of pulmonary tuberculosis which does not meet the above definitions for smear positive TB, in keeping with good clinical and public health practices, diagnostic criteria should include: at least three sputum specimens negative for AFB; radiographic abnormalities consistent with active pulmonary tuberculosis; no response to a course of broad spectrum antibiotics; and a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

Extra-pulmonary tuberculosis

Tuberculosis of organs other than the lungs: *eg*, pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, etc. Disease should be based on one culture positive specimen, or histological or strong clinical evidence consistent with active extra-pulmonary tuberculosis, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

Categories of patients for registration on diagnosis
New: a patient who has never had treatment for TB or has taken anti-tuberculosis drugs for less than one month.

Relapse: a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

Failure: a patient who, while on treatment, is sputum smear positive at 5 months or later during the course of treatment.

Return after default: a patient who returns to treatment with positive bacteriology, following interruption of treatment for two months or more.

Transfer in: a patient who has been transferred from another tuberculosis registry to continue treatment.

Treatment outcome
Cure: a patient who is sputum smear negative in the last month of treatment and on at least one previous occasion.

Treatment completed: a patient who has completed treatment but who does not meet the criteria to be classified as cured or failure.

Treatment failure: a patient who is sputum smear positive at five months or later during treatment.

Died: a patient who dies for any reason during the course of treatment.

Defaulter: a patient whose treatment was interrupted for 2 consecutive months or more.

Transfer out: a patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

Treatment success: the sum of patients cured and those who completed treatment.

Statistical analysis

The data were analyzed by using the statistical software, SPSS version 10. (SPSS Inc, Chicago, Ill, USA). The data with quantitative variables were expressed by median and range while the qualitative variables were estimated by frequency and percentage. Statistical analysis was estimated using either chi-square test or Student's *t*-test as appropriate. A p-value of <0.05 was regarded as statistically significant.

RESULTS

Table 1 demonstrates the socio-demographic characteristics of the study subjects at the time of diagnosis. Patients in the TBDM group were significant older (51.5±12.02 years, range 18-88) than in the TB group (37.5±15.4 years, range 14-95) and had a higher male: female ratio (2.2:1 *vs* 1.9:1). Age-group wise, the significant proportion of TB appeared to increase steadily with age in diabetic patients compared to non-diabetic ones. However, they showed similarities in term of sex, race, marital status, present address, and occupation. Among the determining factors, a lower proportion of patients in TBDM group had consumption of alcohol (0.5%), intravenous drug use (3.6%), BCG vaccination (44.1%) and positive tuberculin skin tests (32.4%). However, we found that TBDM patients showed similar findings in history of previous tuberculosis (6.8%) as well as contact with TB patients (18.5%) as compared to non-diabetics.

For disease location in TBDM patients, the lung was the most common location (91.4%) that occurred in the TBDM group. The chest radiograph reports of 230 cases in the study group and 1,226 cases in the

Table 1
The socio-demographic characteristics of 1, 651 patients attended at National Tuberculosis Center (NTBC) from January 2001 to December 2002.

Variables	TB group (1,410) No. (%)	TB DM group (241) No. (%)
Range of age	14-95 years	18-88 years
Mean ± SD [a]	37.5±15.4 years	51.5±12.02 years
Sex ratio (M:F)	1.9:1	2.2:1
Age group [a]		
≤24	308 (22)	2 (0.8)
25-34	423 (30)	15 (6.2)
35-44	269 (19.1)	43 (17.8)
45-54	192 (13.6)	91 (38)
≥55	218 (15.5)	90 (37.3)
Sex		
Male	917 (65)	167 (69.3)
Female	493 (35)	74 (30.7)
Race[a]		
Malay	697 (49.4)	106 (44)
Chinese	318 (22.5)	73 (30.3)
Indian	149 (10.6)	42 (17.4)
[1]Other	246 (17.4)	20 (8.3)
Marital status [a]		
Single	633 (45)	23 (9.5)
Married	777 (56)	218 (90.5)
Address		
Kuala Lumpur	783 (55.5)	136 (56.4)
Outsider	627 (45.5)	105 (43.6)
Occupation[a]		
Laborer	345 (24.5)	38 (15.7)
Non-laborer	392 (27.8)	51 (21.2)
Unemployed	673 (47.7)	152 (63.1)
Determining factors		
Smoking		
Yes	406 (29)	75 (31.1)
No	1,004 (71)	166 (69.9)
Drinking alcohol		
Yes	10 (0.7)	2 (0.8)
No	1,400 (99.3)	239 (99.2)
Smoking and drinking alcohol		
Yes	72 (5.1)	9 (3.7)
No	1,338 (94.9)	232 (96.3)
Intravenous drug user [a]		
Yes	58 (4.1)	3 (1.3)
No	1,352 (95.9)	238 (98.7)
Case category		
New case	1,307 (93)	226 (94)
History of previous tuberculosis		
Relapse	67 (5)	12 (5)
Return after default	36 (2.5)	3 (1.3)

Table 1 (Continued)

Variables	TB group (1,410) No. (%)	TB DM group (241) No. (%)
History of contact with tuberculosis patients		
Yes	273 (19.4)	46 (19.1)
No	1,137 (80.6)	195 (80.9)
BCG vaccination [a]		
Yes	735 (52.1)	104 (43.2)
No	347 (24.6)	77 (32)
No information	328 (23.3)	60 (25)
Tuberculin skin test (≥ 10 mm)		
Yes	521 (37)	79 (33)
No	254 (18)	48 (20)
No information	635 (45)	114 (47.3)

[1]Other: foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.

[a] $p < 0.05$ for differences between TBDM and TB groups by 2 samples *t*-test or χ^2 test

SD = standard deviation

control group were thoroughly reviewed. However, both groups had similar findings, with opacities or cavities and/or upper lobe involvement as the predominant features. In the diabetics, there were 164 cases with opacities or cavitary disease; 146 (89%) cases involved the upper lobe. In the control subjects, there were 895 cases with opacities or cavitary disease, and 810 (91%) cases involved the upper lobe. In extra-pulmonary tuberculosis, osteoarticular disease was the most common form found in diabetics, whereas, lymph node was the predominant site in non-diabetic patients as presented in Table 2.

This study further revealed the role of treatment and outcome of these patients. Interestingly, we found the treatment success and cure at ≥ 6 months in PTB (38.4%) and at ≥ 9 months in EPT (4.6%) were more common in the TB patients, whereas, the TBDM group showed a higher rate of treatment success and cure (33.3%), particularly pulmonary tuberculosis in the longer duration (≥ 9 months). A lower proportion (19.8%) of the TBDM group defaulted in their treatment and experienced less MDR-TB (1.4%) compared to non-diabetics as demonstrated in Table 3.

DISCUSSION

We comparatively looked at socio-demographic factors that determined the differences between these two groups. This study clearly showed that the greater the age, the more TB was found in diabetic patients (Liu, 1989; Yamagishi *et al*, 1996; Tamura *et al*, 2001). This coincides with the fact that compromised hosts have increased susceptibility due to aging, advances of medical technology or changes in the dietary life and social life. Concomitantly, the proportion of compromised hosts in the patients with tuberculosis has also increased (Yamagishi, 2001), particularly diabetes mellitus as one of the most frequent metabolic distortions (Mugasi *et al*, 1990; Morris *et al*, 1992; Schubert and Heesemann, 1995; Lin *et al*, 1998; Chukanova *et al*, 2000). Moreover, we found that male gender predominated in both groups; however, a slightly higher proportion of tuberculosis was noted in diabetic patients. Our finding is supported by a previous reported study (Mboussa *et al*, 2003). The possible explanations that predisposed diabetics to a higher transmission rate of *M. tuberculosis* have been documented by various studies (Bener, 1990; Liaw *et al*, 1995; Diwan and Thorson, 1999). On the other hand, female patients in both groups seemed to have a much lower proportion of tuberculosis compared to their counterpart (Chan-Yeung *et al*, 2002; Pérez-Guzmán *et al*, 2003). Malaysia is considered a developing country and regarded as having an intermediate level of tuberculosis burden. Therefore, we agree to the certain extent that the possibility of under-diagnosis and under-notification, with consideration of socio-economic and cultural conditions, might play a role at least in non-diabetic patients – a finding consistent with other studies (Connolly and Nunn, 1996; Borgdorff *et al*, 2000). In

Table 2
Disease location of TBDM patients in this study.

Disease location	TB patients (1,410) No. (%)	TBDM patients (241) No. (%)
Tuberculosis (1,333)		
Lung	1,115 (79.1)	218 (90.5)
PTB and disseminated forms (123)	111 (8)	12 (5)
Lung +one site of involvement		
Lung + lymph node	47 (3.3)	2 (0.8)
Lung + pleura	22 (1.6)	2 (0.8)
Lung + bone (spine, hip, knee and ankle)	10 (0.7)	1 (0.4)
Lung + abdomen	7 (0.5)	2 (0.8)
Lung + larynx	4 (0.3)	1 (0.4)
Lung + bronchus	3 (0.2)	1 (0.4)
Lung + genitourinary tract	3 (0.2)	2 (0.8)
Lung + brain	2 (0.1)	-
Lung + skin	1 (0.07)	-
Lung + nasopharynx	1 (0.07)	-
Lung + eye	-	1 (0.4)
Lung + heart	1 (0.07)	-
Lung + epiglottis	1 (0.07)	-
Lung + ≥ 2 sites of involvement	9 (0.6)	-
Extrapulmonary site (195)	184 (13)	11 (4.6)
Lymph node	83 (6)	1 (0.4)
Miliary/disseminated	37 (2.6)	1 (0.4)
Pleura	22 (1.6)	3 (1.3)
Bone and joint	20 (1.4)	4 (1.7)
Abdomen	6 (0.4)	-
Genitourinary tract	6 (0.4)	2 (0.8)
Skin	4 (0.3)	-
Others (eye, heart, muscle, and breast)	8 (0.6)	-

this context, the prevalence of tuberculosis in diabetic patients is still high; in addition, diabetes remains a significant risk factor and its complications affect the epidemiological trends of tuberculosis in this part of the world.

From this study, pulmonary tuberculosis was considered the most common form found in diabetic patients and it showed a much higher proportion than non-diabetic ones. The former observation is supported by those reported in previous studies (Yamagishi *et al*, 1996; Nakamoto and Saito, 1998; Borgdorff *et al*, 2000); however, the latter is contrary to one study (Pérez-Guzmán *et al*, 2003). This indicates that the presence of diabetes mellitus continues to play an important role in the development of pulmonary tuberculosis (Yamagishi *et al*, 2000). Moreover, the relative risk of developing PTB in non-insulin dependent diabetes mellitus (NIDDM) is 5 to 7 times higher and in insulin dependent diabetes mellitus (IDDM), the risk is 26 times highher than the general population of the general population (Kim *et al* 1995; Feleke *et al*, 1999). We examined the radiological appearance of tuberculosis in diabetic patients, which showed similarity with the control cases; both had predominantly upper lobe involvement. This finding is supported by those reported in previous studies (al-Wabel *et al*, 1997; Bashar *et al*, 2001) but contrary to others (Marais, 1980; Morris *et al*, 1992; Bacakoglu *et al*, 2001). Nevertheless, we support that all patients with diabetes should undergo routine chest X ray examination at diagnosis and whenever they develop prolonged cough, fever, or unexplained ill health (Ismail, 2004). In addition, PTB should be suspected

Table 3
The anti-tubercular therapy and outcome of TBDM patients compared to TB patients.

Duration	TB group (1,410)		TBDM group (241)		Total
	PTB [a] No (%)	EPT [b] No (%)	PTB No (%)	EPT No (%)	
At least 6 months					
≥ 6 months	540 (38.3)	35 (2.5)	64 (26.5)	1 (0.4)	640
≥ 9 months	231 (16.4)	65 (4.6)	78 (32.4)	2 (0.8)	376
≥ 12 months	87 (6.2)	35 (2.5)	34 (14.1)	4 (1.7)	160
Total	858 (61)	135 (9.6)	176 (73)	7 (2.9)	1,176
Less than 6 months					
Continuing	16 (1.1)	-	2 (0.8)	-	18
Transfer out	71 (5)	9 (0.6)	10 (4.2)	-	90
Defaulted	281 (20)	40 (3)	42 (17.4)	4 (1.7)	367
Total	368 (26)	49 (3.4)	54 (22.4)	4 (1.7)	475

[a]Pulmonary tuberculosis and disseminated forms; [b] Extrapulmonary tuberculosis
Drug susceptibility testing in the TB group: fully sensitive 1,404 (99.6%); resistance to 1 drug 1(0.07%) and multi-drugs resistance 4 (0.3%)
Drug susceptibility testing in the TBDM group: fully sensitive 239 (98.6%); multi-drugs resistance 2 (0.8%)

in diabetics even if the radiological features are atypical, particularly with lower lung field involvement (Perez-Guzman *et al*, 2001). In extra-pulmonary tuberculosis, osteoarticular disease was the most common form found in diabetics, whereas lymph node disease was the predominant site in non-diabetic patients. Extra-pulmonary tuberculosis was not nearly as common as pulmonary TB, as revealed in this study. One study found that a case may be made for early empirical therapy to cover this organism if there is sufficient clinical suspicion based on the presenting signs and symptoms as well as the pattern of organ involvement (Cunha, 1998).

Our data also showed the overall cure or treatment completion rates of tuberculosis at 6, 9 and 12 months were 76% in TBDM and 71% in TB patients. Interestingly, a higher percentage of TBDM patients occurred although treatment was usually more prolonged, particularly for those with pulmonary tuberculosis as compared to TB patients. In fact, PTB is not only the primary source of infection but also its longer treatment provides a better prognosis among immunocompromized patients. Chemoprophylaxis is considered necessary to prevent the development of tuberculosis in diabetics. Moreover, it should be given only when healing of tuberculosis has been found despite the history of treatment for tuberculosis being absent (Yamagishi, 2001). A higher percentage of non-diabetic patients defaulted in treatment as well. The possible explanation is either they were unemployed or had MDR-TB; however, such trends occurred in both groups and therefore deserve further investigation before any conclusion can be made. From this study, we found only 2 (0.8%) TBDM patients developed resistance to anti-tubercular agents; however, once patients had a confirmed diagnosis of MDR-TB, they were more likely to be enrolled in DOT programs that closely monitor therapy. This observation showed a lesser impact compared to one previous study, which showed a significant association between diabetes and MDR-TB (Bashar *et al*, 2001). There are some hypotheses to explain the possible factors contributing to MDR-TB, such as non-compliance, incomplete treatment, homelessness, and infection with the HIV virus (Brundney, 1991; Frieden *et al*, 1993; Concato and Rom, 1994). Hence, we suggest that drug susceptibility should be strictly screened in all newly diagnosed TB patients complicated with diabetes mellitus. Moreover, if resistance to isoniazid and rifampin is detected, an anti-tuberculosis regimen with at least two new drugs, including an injectable drug tailored to the resistance pattern, is recommended (Harkin and Harris, 1996). No relapse cases were found among TBDM patients; nevertheless, one study showed that recurrences were found only in patients with co-existent diabetes mellitus and tuberculosis compared to other conditions (Mos-Antkowiak, 1991).

This study further showed a poor prognosis once relapse takes place. Therefore, plasma glucose control should be strictly monitored (Kado *et al*, 1992) and an initial intensive phase of an anti-tubercular regimen (four-drug combination) is the preferred treatment for the patients with DM (Kameda *et al*, 1990).

In conclusion, tuberculosis had a significant impact and predominated in male patients coexisting with diabetes mellitus. Pulmonary tuberculosis was the most common disease location and chest X-ray findings were an important tool in its diagnosis. Moreover, a longer period of anti-tubercular treatment meant a better prognosis among these patients. A small number of MDR-TB patients were found; furthermore, no relapses or deaths were discovered in this study.

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