Role of Diabetes Mellitus on Adverse Drug Reaction to Anti-tuberculosis Drugs

ABSTRACT

TB is one of the leading cause of death among infectious diseases. The dual burden of TB and diabetes mellitus (DM) is a major economic and health concern. Anti-TB therapy may predispose patients to develop adverse drug reaction (ADR). The effect of DM on anti-TB ADR requires more studies.

Methods: We performed a cross-sectional study and followed patients for at least two years. Patients were selected from three Malaysian teaching hospitals. TB patients, and diabetic patients with TB were divided into two groups of 200 subjects each. Data were obtained from patients' medical files at the beginning and end of the study period. Prevalence of serious adverse drug reaction (ADR) requiring dose adjustment was assessed.

Results: ADR in our subjects was documented in the medical records and confirmed by a system known as Challenge. The prevalence rates of ADR amongst DM-TB and TB only patients were 16.5% and 14.8%, respectively, but the difference was not significant (Fisher E.T: $P > 0.05$). ADR was more frequent with streptomycin treatment, partially because of its painful administration. Isoniazid treatment showed the least frequency of ADR.

Conclusions: Although the frequency of ADR was high among DM-TB patients, it was not significantly different to that among TB only patients.

ABBREVIATIONS

ADR: Adverse Drug Reaction
DM: Diabetes mellitus
EMB: Ethambutol
GHPP: General Hospital Plu Penang
GIT: Gastrointestinal Tract
HUSM: Hospital of Universiti Sains Malaysia (HUSM),
INH: Isoniazide
PZA: Pyrazinamide
SM: Streptomycin
TB: Tuberculosis
UMMC: Universiti Malaya Medical Centre

1. INTRODUCTION

Tuberculosis (TB) is bacterial infectious disease caused by *Mycobacterium tuberculosis*. TB is one of the leading cause of death among infectious diseases. TB mainly affects disadvantaged-lower class population. Even within rich countries, TB mainly affects people with a lower level of education [1] and income [2]. Although an appropriate combination of anti-TB drugs could cure 95 percent of tuberculosis and the widespread application of the only available vaccine, Bacille Calmette Guerin (BCG), tuberculosis is still out of control in certain areas of the world, TB remains in the top 10 fatal diseases [3].

Diabetes mellitus (DM) is known to be one of the medical risk factor for TB. Although the reason is not yet well explained, diabetic patients are more susceptible to infectious diseases, including tuberculosis, than are non-diabetic subjects [4, 5]. The dual burden of TB and DM is a major economic and health concern. DM negatively affects treatment of TB patients [6, 7]. Anti-TB therapy may predispose patients to develop adverse drug reaction (ADR). The effect of DM on anti-TB ADR requires more studies. In this study, we wanted to discover the prevalence of ADR in TB patients, and the effect of DM comorbidity.

2. METHODOLOGY

The methodology of this study is published elsewhere [6]. Briefly we performed a cross-sectional study and followed patients for at least

two years. Patients were selected from three Malaysian teaching hospitals: General Hospital Plu Penang (GHPP), Universiti Sains Malaysia (HUSM), and Universiti Malaya Medical Centre (UMMC). The study was approved by the Clinical Research Centre of GHPP [(6) dim.SL/CRC/HPP/05], the ethical committee of the UMMC (S13/05/12-2005), and the manager of the HUSM (HUSM/11/020). TB patients, and diabetic patients with TB were divided into two groups of 200 subjects each. Data were obtained from patients' medical files at the beginning and end of the study period. The possible relationships between demographic variables (age, gender and race) and the ADR were studied. Within the same group, the demographics of patients who developed ADR are compared with those that did not develop ADR. Prevalence of serious adverse drug reaction (ADR) requiring dose adjustment or termination of medicine was assessed. SPSS, version 11.5 was used for data analysis. Chi-square and Fisher's Exact Test were used for the analysis of categorical variables like race, gender, or ADR depending expected values of cells as well as size of the tables. Two tailed t-test was used for parametric numerical data like age and weight. Statistical significance was achieved when $P \leq 0.05$.

3. RESULTS

All study centers were following WHO recommended anti-TB drugs and doses. Directly Observed Therapy using short course chemotherapy (DOTS) was followed. First line drugs used were isoniazid (INH), rifampicin (RIF), ethambutol EMB), pyrazinamide (PZA), and streptomycin (SM). INH and RIF were prescribed for nearly all patients (Table 1). During the intensive treatment courses, almost all the patients were getting daily doses of the first line anti-TB medicines that contained 3-5 drugs, including INH and RIF. During the continuation phase, a biweekly regimen of isoniazid and rifampicin was followed. UMMC was using anti-TB drugs on a daily basis for the whole course of the treatment, including the continuous phase. In terms of TB treatment outcome, however, no difference was detectable between daily doses and biweekly doses during the continuous phase. Pyridoxine tablets, as a prophylactic agent against INH side effects, was prescribed for all patients during the whole course of the chemotherapy. Although no multiple drug resistant cases were seen, one case showed resistance to rifampicin, and ofloxacin was prescribed.

Drug adverse reactions in our subjects were documented in the medical records and confirmed by a system known as challenge. When adverse drug reaction is suspected, all anti-TB drugs were stopped; and after a drug washout period, the drugs were reinitiated. First step was to restart single drug with lowest possible dose and the dose was up titrated until clinically effective level was reached. If the patient could tolerate the first drug, then the second drug was added following the same manner as the first drug until all prescribed drugs were checked. The drug that cannot be tolerated was stopped. About 16.5% of DM-TB patients and 14.8% of TB only group experienced major adverse drug reaction. However, the difference between the two groups was not significant, and may require larger sample size (see Table 2).

Drug adverse reactions included ototoxicity, hepatotoxicity, allergy, visual acuity disturbance, cholestasis, and others (Table 2). Allergy, hepatitis, and pain at site of streptomycin administration were most frequent. Streptomycin showed the highest frequency of ADR, while INH and RIF were the safest drugs. Two patients in the DM-TB group and 4 patients in the TB only group developed sensitivity to more than one drug. Regarding the number of ADR, 3 DM-TB patients, and 6 in the TB only group developed more than one ADR (Table 3).

Regarding demographic-related variables like age, gender or race, no difference was seen between the patients presenting with ADR and those without the condition of the same group (Table 4).

Table 1. Anti-TB Drugs and Doses Prescribed for Study Patients

	Anti - TB drugs				
	INH	**RIF**	**PZA**	**EMB**	**SM**
Doses (mg/kg)	5.4mg	10.5mg	24mg	19mg	16mg
% Prescribed	99.7%	100%	93%	52%	66%

Table 2. ADR of Anti-TB Drugs

DM- TB (188 patients)			TB only (196 patients)		
Anti-TB Drugs	**Patients Received**	**Patients developed ADR (%)**	**Anti-TB Drugs**	**Patients received**	**Patients Developed ADR (%)**
SM	106	16 (15)	SM	111	14 (12.6)
PZA	178	10(5.6)	PZA	189	9 (4.7%)
EMB	87	0(0)	EMB	83	4 (4.8%)
INH	187	3(1.6)	INH	196	3 (1.5%)
RIF	188	3(1.6)	RIF	196	3 (1.5%)
Unknown	3	3	Unknown	2	2
Total*	31 (16)		Total*	29 (14.8%)	
P-value > 0.05					

Types of ADR	**Drug Induced**	**Frequencies**	**Types of ADR**	**Drug Induced**	**Frequencies**
Allergy	SM	6	Allergy (total 11)	SM	2
	PZA	5		PZA	5
	RIF	1		EMB	1
				INH	1
Painful injection	SM	5		RIF	1
Hepatitis	RIF	2		UK	1
	INH	1	Painful injection	SM	4
	PZA	4	Hepatitis	PZA	2
	SM	1		SM	2
	UK	2		EMB	1
Ototoxicity	SM	4		INH	1
Nephrotoxicity	SM	1	Ototoxicity	SM	5
				RIF	1
Eye Equity	INH	1	Eye Equity	EMB	2
Neuropathy	INH	1	Nephrotoxicity	SM	1
Uric Acid	PZA	1	Elevated Uric Acid	PZA	1
			Gastritis	RIF	1
				INH	1
				PZA	1

**Some patients were sensitive to more than one anti-Tb drug*

Table 3. Frequency of ADR and Reactivity

DM-TB Patients		**TB only patients**	
Reactivity to Anti-TB Drugs	**Patients**	**Reactivity to Anti-TB Drugs**	**Patients**
Reactive to one drug	29	Reactive to one drug	25
Reactive to two drugs	2	Reactive to two drugs	4
Number of ADR	**Patients**	**Number of ADR**	**Patients**
One ADR	28	One ADR	23
More than one ADR	3	More than one ADR	6
Total ADR	34	Total ADR	36

Table 4. Demographics of all study patients and those who developed ADR within the same group

DM-TB (all study patients)		**DM-TB (patients developed ADR)**	
Race	**Number (%)**	**Race**	**Number (%)**
Malay	97 (49.2)	Malay	12 (39)
Chinese	76 (37.1)	Chinese	13 (42)
Indian	27 (13.7)	Indian	6 (19)

	P-Value (X^2)		> 0.05
Sex	Number (%)	Sex	Number (%)
Male	144 (72)	Male	19 (61.3)
Female	56 (28)	Female	12 (38.7)
	P-Value (X^2)		> 0.05
Age	55.1 (12.4)	Age	54 (12)
	P-value > 0.05		

TB only (all study patients)		**TB only (patients developed ADR)**	
Race	Number (%)	Race	Number (%)
Malay	124 (62)	Malay	18 (62)
Chinese	55 (27.5)	Chinese	9 (31))
Indian	21 (10.5)	Indian	2 (6.9)
P-Value (X^2)		> 0.05	

Sex	Sex	Sex	Number (%)
Male	116 (58.3)	Male	13 (44.8)
Female	83 (41.7)	Female	16 (55.2)
P-Value (X^2)		> 0.05	
Age	44.4 (19.2)	Age	41.8 (SD = 16.8)
		P- Value > 0.05	

4. DISCUSSION

In general, few studies assessing the role of DM on anti-TB related ADR have been published. In the current study, prevalence of ADR was 16% and 14.8% for DM-TB and TB only patients, respectively. However, the difference was not significant. Very different results were reported by D Duangrithi et al. [8]. The frequencies of ADR due to anti-TB drugs varied widely and ranged from 8.3% to 74% in TB only patients, while prevalence of up to 98% was reported in cases with DM comorbidity. B. E. Gu¨lbay et al. reported 8.3% for all TB patients [9]. XQ Han *et a*l. reported 74% and 98% of ADR in TB only and DM-TB, respectively [10], while Siddiqui et al. reported 71% and 92% respectively [7]. This variation might have resulted from the methods of study. In our study, serious cases of ADR were documented, while XQ Han et al. [10] and Siddiqui et al. [7] recorded all types of ADR. Also it is possible that certain symptoms attributed to ADR might have resulted from other diseases or drugs other than anti-TB agents.

Qualitatively, types of ADR in our study included allergy, hepatitis, and others. These reactions match those reported in the literature. In our study, ADR was more frequent with SM treatment, partially because of its painful administration, while INH and RIF showed the least side effect. This finding accords with the report of B. E. Gu¨lbay et al. [9]. In terms of frequency, we found allergy as the most common ADR, followed by hepatitis, and pain at the site of SM administration. A Farazi et al. [11] found hepatitis as the leading ADR followed by GIT, skeletal muscle, and allergy, in descending order.

In our study, no relation was seen between ADR and age, gender or race .This finding is in accord with that of B. E. Gu¨lbay et al. [9], but contrary to the Siddiqui [7] report that males were more susceptible to anti-TB ADR, and A Farazi et al. [11] who reported higher frequencies in females.

Regarding reactivity, 2 patients in the DM-TB group and 4 patients in the TB only group were reactive or sensitive to more than one anti-TB agent. However, no similar reports stating the number of anti-TB agents reacting with a single patient were retrieved from the literature. Three patients in the DM-TB group and 6 patients in the TB only group developed more than one ADR; this is much less than reported by A N Siddiqui et al. [7], where 80% of patients experienced more than one ADR.

5. STUDY LIMITATIONS

The patients' information was retrieved from medical records, which can contain incomplete data.

6. CONCLUSION

No difference was seen between diabetic and non-diabetic TB with respect to ADR. Also no relation was seen between ADR and age, gender, or race. Patients were more reactive to SM, while INH and RIF were safer agents. In

terms of types of ADR, allergy was the most frequent.

REFERENCES

1. Lien LT, Hang NTL, Kobayashi N, Yanai H, Toyota E, et al. (2009) Prevalence and Risk Factors for Tuberculosis Infection among Hospital Workers in Hanoi, Viet Nam. PLoS ONE 4(8): e6798. doi:10.1371/journal.pone.0006798
2. Oxlade O, Murray M (2012) Tuberculosis and Poverty: Why Are the Poor at Greater Risk in India? PLoS ONE 7(11): e47533. doi:10.1371/ journal.pone.0047533
3. WHO, "Cummunicable Disease: Tuberculosis Fact Sheet," 2016, http://www.searo.who.int/en/Section10/Section2097/ Section2106 10682.htm.
4. Boucot, K. R. (1957). Diabetes mellitus and pulmonary tuberculosis. *Journal of Chronic Diseases, 6*(3), 256-279.
5. Masoodi, S. R., Wani, A. I., Misgar, R. A., Gupta, V. K., Bashir, M. I., & Zargar, A. H. (2007). Pattern of infections in patients with diabetes mellitus--Data from a tertiary care medical centre in Indian sub-continent. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 1*(2), 91-95.
6. Syed Azhar Syed Suleiman, Daud M. Ishaq Aweis, Ali Jimale Mohamed, Abdul RazakMuttalif, and Mohamed A. A. Moussa. (2012), Role of Diabetes in the Prognosis and Therapeutic Outcome of Tuberculosis. *International Journal of Endocrinology*, vol. 2012, Article ID 645362, 6 pages, 2012. doi:10.1155/2012/645362.
7. AN Siddiqui et al. (2016), Effect of Diabetes Mellitus on Tuberculosis Treatment Outcome and Adverse Reactions in Patients Receiving Directly Observed Treatment Strategy in India: A Prospective Study. BioMed Research International Volume 2016, Article ID 7273935, 11 pages http://dx.doi.org/10.1155/2016/7273935
8. D Duangrithi - 2013, Impact of diabetes mellitus on clinical parameters and Treatment outcomes of newly diagnosed pulmonary tuberculosis patients in Thailand. Int J Clin Pract. 2013 Nov; 67(11):1199-209. doi: 10.1111/ijcp.12215. Epub 2013 Jun 10.
9. B.E. Gu¨lbay et al. (2006), Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respiratory Medicine (2006) 100, 1834–1842
10. XQ Han et al. (2017), Prevalence and Risk Factors Associated with Adverse Drug Reactions among Previously Treated Tuberculosis Patients in China. Biomed Environ Sci, 2017; 30(2): 139-142.
11. A Farazi et al. (2014), Adverse Reactions to Antituberculosis Drugs in Iranian Tuberculosis Patients. Tuberculosis Research and Treatment Volume 2014, Article ID 412893.