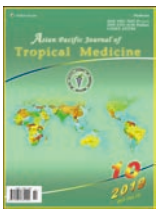

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Glycemic control in tuberculosis: Lessons learned from Taiwan

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ABSTRACT

The global epidemic of diabetes and tuberculosis poses challenges to the control of both diseases. Patients with tuberculosis and diabetes experience worse clinical manifestations, increased risk of treatment failure, recurrence, and death. Diabetes is also associated with risk for latent tuberculosis infection. Management of hyperglycemia reduces the risk and improves the outcome of tuberculosis in diabetic patients. Recent epidemiological studies from Taiwan have provided new and important information on the benefits of metformin in tuberculosis. When addressing the issue of multidrug-resistant tuberculosis, a shortened anti-tuberculous therapeutic regime seems a feasible approach for better cure rates, with less loss-to-follow.

1. Introduction

Tuberculosis (TB) is still a major global health problem. The latest WHO report estimates that almost 23% of the world's population is infected with *Mycobacterium* (*M.*) *tuberculosis*, with 10 million new cases infected each year, and more than 1.3 million per year in the world[1,2]. In countries with low and moderate incidence of TB, the disease tends to concentrate in certain groups, such as the diabetic population[3]. The global epidemic of obesity and diabetes mellitus (DM) is also affecting a great amount of the world population, rising at an insidious and alarming pace, especially in low- and middle-income countries.

Presence of both conditions is of particular concern, since patients with TB and DM experience worse clinical manifestations, increased risk of treatment failure, recurrence, and death[4-6]. DM is also associated with risk for latent TB infection[7].

Several studies addressing TB in DM patients have been recently conducted in Taiwan in the past ten years. This new literature provides new and important information on the benefits of correcting hyperglycemia in TB.

2. TB and diabetes in Taiwan

With a population of more than 23 million residents, Taiwan is endemic for TB. The incidence of TB in Taiwan, however, has been constantly declining since 2005[8]. Despite the fact that the disease burden caused by TB is falling in most countries, it is not occurring at a pace fast enough to meet the milestones of the End TB Strategy[9], nor the 95% reduction by 2035[1]. Computer modelling predicts that lowering the prevalence of DM could accelerate the decline of TB incidence and reduce mortality[10].

In Taiwan, DM is the most important risk factor for developing pulmonary TB[11]. After adjusting for confounding factors, type 2 DM was found to be an independent risk factor for TB nationwide[12]. Association seems to be stronger for type 1 DM (hazard ratio 4.23)[13] than for type 2 DM (HR 1.31)[12]. Poor glycemic control, however, can increase the hazard ratio to 3.38 in adults less than 65 years old[14]. Men appear to have a higher risk than women[15]. Patients with ages of 55-64 years have the highest association of DM (*OR*=3.53) compared with those under

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45 years[16]. TB patients with heart failure, ischemic heart disease, cerebral vascular disease, hypertension, dyslipidemia, chronic kidney disease, and liver disease were more likely to associate with DM compared to those without the variables[16].

Incidence of DM in Taiwan has been rising in children less than 15 years old[17]. The prevalence of DM has been progressively increasing in Taiwan in the decade 2000-2010, with an average prevalence rate of 27.9%[16]. Prevalence of DM in Taiwan can range from 4%-10% in normal adult population[18,19] to 15% and 43% in patients with chronic kidney disease[18] and heart failure[20], respectively. A population-based cohort study showed that chronic kidney disease and DM are associated with an increased risk of developing pulmonary TB, with a hazard ratio of 1.45 and 1.34, respectively[21], confirming previous results[21]. When TB and DM are both present, there is a higher incidence of chronic kidney disease[22]. Diabetic complications such as renal insufficiency complicates the treatment of TB as some anti-TB drugs are cleared by the kidney[23].

DM still poses a huge risk for TB in other cohorts, such as patients with depression[24]. After adjusting for other potential confounders, DM is also associated with increased risk of TB relapse[25], and recurrence[6]. The paradox of obese population does not present an increased risk of TB, despite being more likely to be diabetic[26].

Variations in disease presentation are likely the result of interaction or additive effects between the contribution of diabetes to immune dysfunction and a variety of additional host factors, *e.g.* smoking, could also affect immunity[27]. In fact, smoking appears to have joint effect in diabetes to develop active TB[28]. DM impacts the natural history of TB due to the dysfunctional innate and adaptive immunity in the diabetic patient[27]. TB disease appears to have a more severe presentation in DM patients, judging from radiological findings. Extensive parenchymal lesions, large non-cavitary nodule, multiple cavities, large cavities unusual location, and whole lobar involvement are more common in DM patients[29,30].

TB incidence and TB-related mortality has been in decrease. The death rate of TB patients is approximately 20% in Taiwan[31]. In newly-diagnosed TB patients in Taiwan, those with DM has a higher incidence density of mortality than non-DM TB patients[32]. DM is still listed as the fifth leading cause of death in Taiwan[33].

3. Glycemic control in TB

It has been shown that appropriate TB treatment in patients with DM leads to better glycemic control[34]. It has been proposed that TB disease may induce hyperglycemia through various mechanisms[35]. Anti-TB treatment may serve to lower blood glucose levels, even in euglycemic patients at baseline. Antidiabetic treatment may still be a contributing factor to reverse hyperglycemia, in this scenario of infection-induced stress dysglycemia[35].

Chronic hyperglycemia is associated with dysfunctional immunity to *M. tuberculosis* and also affects the microvasculature by reducing lung tissue perfusion for optimal immune surveillance in diabetic patients[36]. A cohort study in northern Taiwan found that diabetic patients with poor glycemic control (FPG>130 mg/dL) had a significantly higher hazard of TB, with an adjusted hazard ratio of 2.21, compared to those without DM. Most importantly, this study also showed that the hazard of TB in diabetic patients with good glycemic control (FPG <130 mg/dL) did not differ significantly from that in nondiabetic individuals[14]. This validates the findings of a previous transversal study in the same area showing that diabetic patients with hemoglobin A1c>7% were significantly more likely to be *M. tuberculosis* smear positive as compared with non-diabetic patients, but not those with hemoglobin A1c <7%[37].

Management of hyperglycemia reduces the risk and improves the outcome of TB in DM patients[38]. A pay-for-performance program in Taiwan, leading to enhanced case management of DM, reduced the risk and mortality over TB treatment success amongst patients with DM[39].

Recent epidemiological studies from Taiwan have provided new and important information on the benefits of metformin (MET) in TB (Table 1). Use of MET in the initial 2 years decreases the risk of developing active TB[41,43]. This was confirmed through a 12-year longitudinal cohort study, after adjusting for comorbidities, diabetes complications, and anti-diabetic therapy[42]. This decrease in risk appears to be directly proportional to the MET dosage[11,44]. MET can reverse mortality related with DM during TB therapy[40].

Last, a study from Taiwan in a limited number of DM patients, has

Table 1. Metformin usage in tuberculosis patients in Taiwan (2018).

Sample size	Type of study	Major findings	Refs
2 416	Retrospective	DM poses an increased risk of adverse TB treatment outcomes and MET can reverse mortality related to DM during TB therapy	[40]
T2DM 40 179	Retrospective cohort	Use of MET in the initial 2 years decreases the risk of developing active TB	[41]
T2DM 49 028	Longitudinal (12 years)	MET use was an independent factor for predicting a reduced risk of active TB, after adjusting for co-morbidities, DM complications, oral anti-DM therapy type and statin use	[42]
88 866	Retrospective	Decreased risk to develop active TB directly proportional to the MET dosage in a comparison group of low *vs*. high users	[14]
T2DM: 148 468 (MET) *vs*. 15 799 (non-MET)	Retrospective	MET use is associated with a reduced risk of developing TB in a dose pattern in patients with T2DM	[41]

T2DM: Type 2 diabetes mellitus; MET: metformin.

shown promising potential use of the cholesterol-lowering drug, ezetimibe, as an adjunctive therapy for TB[45]. The drug lowered the prevalence of latent, and intracellular lipid contents, as well as the intracellular growth of *M. tuberculosis* in leucocytes from ezetimibe-treated patients with DM[45].

4. Multidrug-resistant TB (MDR-TB)

MDR-TB in Taiwan in the 90s had a 51.2% cured rate, 10.4% treatment failure, 9.4% mortality[46]. Cure rates have improved to 61% in the 21st century in Taiwan[47]. Challenges include treatment interruption in almost 30% of the cases[46], loss of follow up, presence of cancer, chronic kidney disease, and resistance to fluoroquinolone[47]. A shortened MDR-TB treatment regime, such as the short-course plus program to treat MDR-TB patients in Eastern Taiwan has shown a low proportion of loss-to-follow-up (1.2%), resulting in a high treatment success rate[48]. This is probably feasible to the relatively still low rates of pre-extensively drug resistant and extensively drug resistant TB in Taiwan[49].

DM is associated with resistance to isoniazid in Eastern Taiwan[50]. The association between DM and MDR-TB could not be made, possibly due to the sample size, according to authors. A recent meta-analysis of 24 observational studies from 15 countries, including Taiwan suggests that DM can significantly increase the odds of developing MDR-TB[51]. The impact of glycemic control on MDR-TB outcomes is still unknown.

5. Conclusions

DM not only increases the risk of developing active TB, it also affects its clinical presentation and the outcome of treatment. Control of glycemia appears crucial in counterbalancing the negative outcomes of TB. Several studies from Taiwan are starting to show the promising benefits from the use of MET. Diabetes is associated with isoniazid-resistance in. A shortened anti-TB therapeutic regime seems a feasible approach for to cure MDR-TB, as it diminishes loss-to-follow.

Conflict of interest statement

Authors declare no conflict of interest.

Authors' contribution

Conceptualization and article writing (MCW and JLC).

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