Diabetes: A Contributor to Tuberculosis in Tropical Australia

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Abstract. In countries with a high-burden of tuberculosis (TB), it has been well established that there is an increased incidence of TB among patients with diabetes. However, in countries with a low burden of TB there are conflicting reports. This study aimed to determine if diabetes was associated with TB in patients admitted to a teaching hospital in tropical Australia. A 20-year retrospective study found patients with comorbid diabetes were seven times overrepresented in the TB patient population when compared with the general population. This study demonstrates a strong association between TB and diabetes regardless of TB endemicity.

Globally, tuberculosis (TB) is the single leading bacterial cause of death.¹ The increasing emergence of comorbid immune suppressing conditions has accounted for the resurgence in TB.^{2,3} Patients with diabetes and prediabetes have an increased risk of bacterial infections and demonstrate a poorer prognosis.^{4,5} Current estimates reveal patients with diabetes have on average a 3-fold risk of developing active TB when compared with the general population. In some regions, up to 50% of TB is associated with diabetes.^{6,7}

In low-burden TB countries such an association has not been reported and has been attributed to better glycemic control among all patients with diabetes.^{8,9} It has been suggested that the association of TB and diabetes may not be a problem in these countries with a low burden of TB. The prevalence of comorbid TB and diabetes also remains ill-defined in many tropical areas within the Western Pacific region for both low- and high-burden TB countries, warranting further investigations.^{1,8,9} The aim of this study was to determine if diabetes was a risk factor associated with TB in a low-burden tropical region by examining medical records and determining if TB patients had evidence of preexisting diabetes.

We undertook a 20-year retrospective investigation in a defined group of patients with culture-confirmed TB admitted to a tertiary referral hospital in tropical Australia (#QTHS/HREC/43). In total, 69 patients were identified with TB between 1995 and 2014 and included in the analysis. The χ^2 test with Yates correction was used to assess whether a significant association existed between diabetes and TB and clinical outcomes.

Comorbid TB and diabetes occurred in 23.2% ($N = 16$) of patients. There was a significant association between TB and diabetes ($P < 0.0001$) when compared with the general population of the region. Patients with diabetes were seven times overrepresented in the TB patient population (OR = 6.6; 95% CI = 3.788–11.60) in comparison to the general population. Almost half ($N = 7$; 43.8%) of the diabetic patients were recorded as having poorly controlled diabetes, as assessed by fasting blood glucose (> 6.0 mmol/L) and HbA1c levels ($> 6.5\%$).

Overseas-born individuals and indigenous Australians were overrepresented in patients with TB alone and comorbid diabetes when compared with the general population. The majority of overseas-born patients originated from high-risk TB

countries namely Papua New Guinea ($N = 16$), followed by India ($N = 3$), Burma ($N = 2$), and Sudan ($N = 2$). There was a lower proportion of comorbid TB and diabetes compared with solitary TB in patients originating from both high- and low-risk TB countries (high-risk country: 25.0% versus 50.2%; low-risk country: 6.3% versus 6.5%). In contrast, comorbid TB and diabetes was more prevalent than TB in isolation for Australian-born patients (indigenous Australians: 43.8% versus 28.3%; non-indigenous Australians: 25.0% versus 15.1%).

Comorbid diabetes was associated with pulmonary TB ($N = 14$; 87.5%; $P = 0.0103$; OR = 7.84) rather than extrapulmonary disease ($N = 2$; 12.5%). Comorbid diabetes was also associated with smear positivity at TB diagnosis ($N = 13$; 81.3%; $P = 0.0084$; OR = 6.603) when compared with non-diabetic patients. A higher proportion of patients with comorbid diabetes had pulmonary cavitation (31.3% versus 20.3%), relapsed disease (18.8% versus 15.9%), and drug resistance (12.5% versus 7.2%) when compared with non-diabetic patients; however, these did not reach significance.

This patient-based research demonstrated that an association exists between TB and diabetes in a low-burden TB country. The results from this study support the observation that the prevalence of comorbid TB and diabetes may exceed world estimates, even in a tropical area with a low incidence of TB (Table 1).^{9,11} Recent predictions further validate the impact of the growing diabetes pandemic on TB outcomes. It is estimated that up to 7.8 million TB cases and 1.5 million TB deaths could be averted if interventions reduce diabetes by 35% over the next 10 years.¹²

In the past, patients with poorly controlled glycemia have been reported to be more susceptible to active TB, in addition to having more severe disease.¹³ Greater health-care access and better glycemic control among diabetic patients has been attributed to the mitigated TB–diabetes comorbidity in low-burden TB countries.^{8,9} However, in our study more than 40% of patients with comorbid diabetes were reported to have poor glycemic control.

Other clinical-based studies have also found that patients with diabetes have a more severe form of TB and are more likely to succumb to the disease (Table 1).^{10,14,15} In this study, diabetes was associated with pulmonary rather than extrapulmonary TB and smear positivity at the time of TB diagnosis, hence indicating patients with diabetes may pose an increased infection risk to the wider community.^{10,16} These findings are supported by previous studies, which have documented an increased prevalence of pulmonary TB and smear positivity in

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TABLE 1

Comparison of sociodemographic and disease characteristics in patients with comorbid tuberculosis diabetes from different study populations

Patient characteristics (%)	Tropical Australia (current study)	Australia (2012) ⁹	India (2012) ⁷	Central America (2007) ¹⁰
Male:female	1.7:1	1.2:1	3:1	1.7:1
Diabetes	23.2	4.3	25.3	27.8
Prediabetes	Na	Na	24.5	Na
Indigenous	43.8	2	Na	Na
Overseas born	31.3	52	Na	53.7*
Smear positive	81.3	Na	55.8	64.9
Drug resistance	12.5	Na	Na	Na
Pulmonary TB	87.5	Na	87.2	97.8
Extrapulmonary TB	12.5	Na	12.8	2.2
Pulmonary cavitation	31.3	Na	Na	60.4
Relapse/reactivation	18.8	Na	8.6	Na
Death	6.3	Na	Na	Na

TB = tuberculosis; Na = data not provided.

*Patients of Mexican origin, no data available on total overseas-born population.

diabetic patients.¹⁵ It has also been shown that patients with diabetes are at a higher risk of relapse following treatment and have an increased chance of death with TB as a coinfection.¹⁴ In our study, we also found pulmonary cavitation, relapse and drug resistance to be overrepresented in those patients with comorbid TB and diabetes.

The double burden of TB and diabetes has been recognized as a global problem. Even with the limited TB patients encountered over a 20-year period as would be expected in this tropical setting, the results for the first time have demonstrated the association between TB and diabetes in a region with a low incidence of TB. Additional clinical-based retrospective and prospective studies are required to determine if this association extends to other low-burden TB regions and how this comorbidity impacts on disease severity and treatment responses. These observations support the view that screening and subsequent treatment of patients with diabetes for latent TB may be warranted in such settings.

Received April 7, 2015. Accepted for publication April 30, 2015.

Published online June 8, 2015.

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