



## Review

# The global dynamics of diabetes and tuberculosis: the impact of migration and policy implications



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## SUMMARY

The convergence between tuberculosis (TB) and diabetes mellitus (DM) will represent a major public health challenge in the near future. DM increases the risk of developing TB by two to three times and also increases the risk of TB treatment failure, relapse, and death. The global prevalence of DM is predicted to rise significantly in the next two decades, particularly in some of the low- and middle-income countries with the highest TB burden. Migration may add further complexity to the effort to control the impact on TB of the growing DM pandemic. Migration may increase the risk of DM, although the magnitude of this association varies according to country of origin and ethnic group, due to genetic factors and lifestyle differences. Migrants with TB may have an increased prevalence of DM compared to the native population, and the risk of TB among persons with DM may be higher in migrants than in autochthonous populations. Screening for DM among migrants, screening migrants with DM for active and latent TB, and improving access to DM care, could contribute to mitigate the effects of DM on TB.

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## Introduction

Tuberculosis (TB) is now the most common infectious disease cause of death worldwide, and developing countries carry a large burden of the 1.6 million deaths caused by TB every year.<sup>1</sup> The disease burden in developing countries due to non-communicable diseases is also increasing and is no longer limited to communicable diseases. Diabetes mellitus (DM) is a global epidemic disease affecting both the developed and developing countries. Approximately 15% of TB patients have comorbidity with diabetes. The convergence between the ongoing TB epidemic and some non-communicable diseases such as diabetes will present a major public health challenge in the near future.<sup>2</sup> It has been estimated that the global prevalence of diabetes will grow significantly in the coming decades, and this increase may be particularly marked in some of the low-income and middle-income countries with the highest burden of TB.<sup>3</sup> Migration flow from these countries has had a major impact on the global dynamics of both diseases,<sup>4,5</sup> and the complex interaction among migration, TB, and diabetes needs to be addressed in the context of the efforts to make progress towards the ambitious goals of the post-2015 End TB Strategy.<sup>6</sup>

This review summarizes current knowledge on the biological and epidemiological aspects of the association between TB and diabetes and focuses on the interaction of international migration with these two conditions. The available evidence on the impact of migration on the DM–TB co-epidemics is also presented, and the need for specific interventions to tackle this public health problem is discussed.

## The diabetes–tuberculosis co-epidemic

Although the link between type 2 diabetes and TB is well recognized, it is only in the last decade that appreciation of its relevance as a widespread public health problem has become the focus of global attention. Four systematic reviews quantifying the increased risk of developing TB among people with type 2 DM have been published recently, and they show that DM increases the risk of active TB by two to three times.<sup>7–10</sup> Moreover, the severity of DM seems to be related to the magnitude of this risk: insulin-dependence – as a marker of disease severity – predicts increased TB risk,<sup>11,12</sup> and poor glycaemic control has been identified as a risk factor for TB.<sup>13</sup>

## Epidemiological considerations

At the population level, a study by Goldhaber-Fiebert et al., performed between the 1990s and the early 2000s, showed that TB prevalence and incidence were more likely to increase in countries in which diabetes increased.<sup>14</sup> An ecological longitudinal study exploring the relationship between TB and diabetes globally in the period 2000–2012 also found an increase in the prevalence of diabetes with the incidence of TB, although this was limited to countries with high diabetes prevalence rates (> 7.6%), which were primarily on the Asian Continent.<sup>15</sup>

The convergence of the diabetes and TB pandemics represents a new phenomenon in the classic epidemiological transition predicted by Omran in 1971,<sup>16</sup> since the original theory did not predict that elements of globalization and economic development could so quickly generate an ‘age of degenerative diseases’ before

the ‘age of receding pandemics’ was over. Due to the abundance of calorie-dense/low-fibre foods and the adoption of sedentary lifestyles, the diabetes epidemic is rapidly growing, while the spread of TB remains a global public health threat. The comorbidity of TB and diabetes exemplifies an epidemiological transition where chronic diseases occur simultaneously with infectious diseases, “not simply in the same population, but in the same individual”.<sup>17</sup>

It was recently estimated that in 22 countries that carry 80% of the global burden of TB, the proportion of cases attributable to diabetes increased from 10% in 2010 to 15% in 2015,<sup>6</sup> and it was stated that this fraction could grow further in the near future. In fact, current predictions are that the prevalence of diabetes, primarily type 2 diabetes, is set to rise beyond 592 million by 2035,<sup>2</sup> and approximately 80% of these cases will be in low- and middle-income countries, where the disease strikes at younger ages and even lower body mass indexes,<sup>18</sup> and where the prevalence of TB is also high. By 2030, India, China, Indonesia, Pakistan, and Brazil together are projected to have half of the world’s people living with diabetes, and these countries are likely to see the most significant impacts of this co-epidemic in the near future.<sup>14,19</sup>

## Clinical considerations of diabetes–tuberculosis comorbidity

Patients with TB–diabetes appear to have poor TB treatment outcomes. Those TB patients with poor blood sugar control have increased rates of treatment failure, relapse, and death than those with good glycaemic control. Diabetic patients with TB are also more likely to develop multidrug-resistant TB (MDR-TB). Diabetes modifies the clinical presentation of pulmonary TB, is associated with atypical radiological presentation,<sup>20</sup> and increases the risk of failure,<sup>20,21</sup> death,<sup>22,23</sup> reactivation, and relapse.<sup>13,20</sup> Diabetes has been found to be an independent risk factor for higher prevalence or a greater severity of some symptoms, such as cough, haemoptysis,<sup>14</sup> and fever, and delayed sputum conversion.<sup>20,21</sup> Data indicating higher bacillary burden in sputa of diabetic patients are conflicting.<sup>24–26</sup>

## Diabetes, immunosuppression, and increased susceptibility to tuberculosis

It is well known that HIV infection increases the risk of developing TB, and persons living with HIV have an increased risk of metabolic syndromes, which in turn predispose them to diabetes, possibly linked to the use of antiretroviral drugs.<sup>27–30</sup> The relationship between HIV infection and the TB–diabetes comorbidity, however, is still poorly explored, and more studies are needed on this issue.

It is unclear whether diabetes increases susceptibility to initial *Mycobacterium tuberculosis* infection or the risk of progression from TB infection to active disease, but evidence for defects in innate and adaptive immunity of patients with diabetes suggests that this chronic disease can have an impact on both TB stages.<sup>31</sup> Current findings on the underlying biology that promotes the TB–diabetes association support an inefficient innate immunity, followed by a hyper-reactive cellular response to *M. tuberculosis*; however, the contribution of these altered responses to TB susceptibility or to the more adverse clinical outcomes of TB patients with diabetes remains unclear.

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