

## TB and COVID-19: paying attention to diabetes mellitus

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In 2019, global diabetes prevalence was 463 million. Diabetes increases the risk of TB and adverse treatment outcomes including death and relapse. Diabetes also increases the risk of severe disease, multi-organ failure, coagulopathy and death in COVID-19. TB and COVID-19 share many features, suggesting opportunities to integrate prevention, diagnosis and care. Three areas for further work are highlighted: better infection control in diabetes clinics, easier and quicker diagnosis using similar technology platforms and optimal blood glucose control. The funding and resources for COVID-19 should be harnessed to improve TB and diabetes care and achieve their respective sustainable development goal targets.

**Keywords:** COVID-19, diabetes mellitus, SARS-CoV-2, TB

World Diabetes Day in 2020 saw the launch of the Lancet Commission on Diabetes.<sup>1</sup> Using worldwide trend analyses, diabetes prevalence has doubled in men and increased by 60% in women over the last 25 y. In 2019, global diabetes prevalence was 463 million, with 80% of affected people living in low- or middle-income countries.<sup>1</sup>

In 2009, we drew attention in this journal to the link between diabetes and TB and suggested the need for high-quality implementation research to better understand how to screen, care for and monitor people with dual disease.<sup>2</sup> Considerable progress has been made. There is sound evidence that people with type 1 and type 2 diabetes have a two- to three-times higher risk of TB, including drug-resistant disease, compared with the general population, and have higher rates of adverse treatment outcomes that include treatment failure, death and TB relapse.<sup>3</sup> Adverse outcomes are more frequent if diabetes control is poor. In 2011, the WHO and The International Union Against Tuberculosis and Lung Disease (The Union) launched the Collaborative Framework for Care and Control of Tuberculosis and Diabetes, recommending bidirectional screening of the two diseases, especially in high TB-burden countries.<sup>4</sup> In 2019, The Union and World Diabetes Foundation (WDF) published the first Guide to the Essential Practice of Managing Diabetes-Tuberculosis.<sup>5</sup>

In December 2019, a new highly transmissible virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged, engulfing the world in the COVID-19 pandemic with 60 million confirmed cases and 1.4 million COVID-19 deaths reported to date. While some data suggest that people with diabetes are at risk of COVID-19 infection,<sup>6</sup> of more concern is the growing evidence that individuals with diabetes are at a higher risk of more severe disease requiring hospitalisation, multi-organ failure, coagulopathy and death compared with those who do not have diabetes.<sup>7</sup> Obesity, hypertension and ischaemic heart disease frequently accompany type 2 diabetes and people with this metabolic syndrome are particularly at risk of severe disease and death.<sup>8</sup>

TB and COVID-19 share many characteristics. Both are respiratory infections, transmitted from person to person through close contact and in crowded and poorly ventilated places, and they often present with fever and cough. The two diseases can occur concurrently. Individuals with either latent or active TB may be more susceptible to COVID-19, which may in turn be more severe than in individuals without TB.<sup>9</sup> The basic disease control measures for the two diseases are similar: infection prevention and control, early detection of cases and contact tracing. These features suggest that there are opportunities to integrate prevention,

diagnosis and care, particularly in people at high risk of severe disease and death, such as those with diabetes.

A recent assessment of diabetes clinics in China showed inadequate implementation of measures to prevent airborne transmission of tubercle bacilli.<sup>10</sup> The COVID-19 pandemic should now give stronger and more urgent impetus to improving this situation. Measures to reduce transmission of TB and COVID-19 would include more use of telemedicine and digital health platforms to decongest clinics, proper use of natural and/or mechanical ventilation, physical distancing, mandatory wearing of face masks, widespread availability of hand sanitisers and standard operating procedures for screening and prioritising people with cough. Even when an effective COVID-19 vaccine becomes widely available, these measures will still need to be implemented and monitored.

Sputum specimens and nasopharyngeal/oropharyngeal swabs are required for pulmonary TB and COVID-19 diagnosis, respectively, with PCR technology being the preferred methodology. The Xpert MTB/RIF assay using the GeneXpert platform is the recommended initial diagnostic test in people with presumptive TB, and many countries have already deployed this automated, rapid and highly sensitive technology—which also detects rifampicin resistance—in their health facilities. The same platform is now being used for diagnosing SARS-CoV-2 with encouraging results.<sup>11</sup> People with diabetes presenting with cough and fever should be investigated for both COVID-19 and TB, either sequentially or concurrently, and use of the same diagnostic platform simplifies logistics and quickens diagnostic times. Further research is needed to determine whether the same sample type (sputum or saliva) can be used for both infections and how to implement optimal biosafety measures in the diagnostic laboratories. Given the high rates of undiagnosed prediabetes and diabetes worldwide, people diagnosed with TB and COVID-19 in general health facilities and TB centres also need to be screened for hyperglycaemia and concurrent diabetes, as recommended in The Union and WDF guidelines.<sup>5</sup>

Better diabetes control improves TB treatment outcomes.<sup>3</sup> Metformin is the first choice glucose-lowering agent in people with diabetes and TB.<sup>5</sup> The drug also augments host immune responses to *Mycobacterium tuberculosis*, and in Taiwan metformin was associated with significantly decreased mortality during TB treatment, similar to that seen in people without diabetes.<sup>12</sup> Similarly, in individuals with diabetes and COVID-19, well-controlled blood glucose levels are associated with significantly lower mortality rates compared with poorly controlled levels.<sup>7</sup> Further research is needed to determine how best to control blood glucose levels and manage any associated hypertension and metabolic syndrome in people with diabetes and TB/COVID-19, especially in light of evidence that corticosteroids (which disturb glucose metabolism) reduce mortality in critically ill patients with COVID-19.<sup>13</sup>

An example of a health facility providing integrated care for diabetes, TB and COVID-19 is the Shenyang Chest Hospital in the northeastern province of Liaoning, China. Strict infection control measures are applied in all clinics and wards, and people with diabetes and with suspected or diagnosed TB or COVID-19 must wear face masks and observe physical distancing. Before admission to hospital for any reason, all patients must have nasopharyngeal or oropharyngeal swabs taken for SARS-CoV-2 investigation. There is some form of tridirectional screening: all patients

diagnosed with TB are routinely screened for diabetes and COVID-19; all people with diabetes are routinely screened for TB; and patients suspected or diagnosed with COVID-19 are screened for TB. Comprehensive treatment is offered and provided to those with one, two or three of the diseases combined.

There are other areas where research, collaboration and integration around TB, COVID-19 and diabetes can make a difference to prevention, case detection and treatment outcomes. These include assessing innovative home-based care models for people with diabetes so that they can avoid crowded health facilities, training healthcare workers to use suitable algorithms to identify, diagnose and monitor individuals with the three diseases, harnessing community-wide support for testing and contact tracing, as well as better understanding and management of post-TB and post-COVID-19 morbidity and disability. COVID-19 is a new disease, likely to be here for the foreseeable future, and the resources and funding that have been raised and diverted in 2020 to deal with the pandemic are staggering. This must not, however, be to the detriment and neglect of other diseases. The scientific and funding opportunities to mitigate the negative impact of COVID-19 must also be used for better control of TB and diabetes so that we can still achieve our sustainable development goals of ending the TB epidemic and reducing non-communicable disease premature mortality by 2030.

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