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# Latent tuberculosis infection and non-infectious co-morbidities: Diabetes mellitus type 2, chronic kidney disease and rheumatoid arthritis

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ABSTRACT

The prevalence of non-communicable diseases is increasing worldwide, which coincides with the persistence of infectious diseases including tuberculosis. These can synergistically affect individual and population health. Three non-communicable diseases that are relevant because of their associated morbidity, mortality and disability are type 2 diabetes mellitus, chronic kidney disease and rheumatoid arthritis. There is some evidence that patients with these conditions are at increased risk of acquiring latent tuberculosis infection (LTBI) and of this progressing to active disease. Unfortunately, evidence on accurate testing and effective prophylactic treatment in these populations is lacking. This review discusses current evidence and recommendations for management of LTBI in these patients.


## Introduction

In recent decades tuberculosis (TB), like many other infectious diseases, has remained prevalent in many countries around the world (WHO, 2018a). This collides with the burden of non-communicable diseases which, although lower or equal to that of infectious diseases in many regions, is rapidly increasing (Magee et al., 2018). This scenario can jeopardize the goal of TB elimination, of which latent tuberculosis infection (LTBI) control is a fundamental step (WHO, 2014).

The mechanisms behind the development of LTBI are poorly understood: i.e. why some individuals who are exposed to *Mycobacterium tuberculosis* develop LTBI whereas others appear to eliminate the infection and do not exhibit an immune response when tested. This makes it even more challenging to evaluate LTBI in specific populations such as people living with non-communicable diseases. However, some data indicate that the risk of developing LTBI upon exposure to the pathogen is greater in these populations.

In addition, there is growing evidence suggesting that the risk of individuals with LTBI developing active TB is greater in some non-communicable diseases which affect the function of the immune system, namely diabetes mellitus type 2 (DM-2), chronic kidney disease (CKD) and rheumatoid arthritis (RA). To effectively manage this increased risk, data are required to improve the diagnosis, treatment and prevention of LTBI and active TB in patients with these diseases.

### *Diabetes mellitus type 2*

One of the most relevant non-communicable diseases, DM-2, has increased in prevalence in low and middle income countries in recent years. There is evidence of an association between LTBI and DM-2 (Lee et al., 2017). Initial data suggest that there is a large heterogeneity in the prevalence of LTBI among DM-2 patients in different populations, e.g., Indonesia (38.6%) (Koesoemadinata et al., 2017) or Mexico (51.3%) (Martinez-Aguilar et al., 2015). However, most of the studies that evaluated LTBI prevalence

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among DM-2 patients did not compare this against LTBI prevalence in the general population, leaving room to more accurately quantify the excess of LTBI in DM-2 patients. This association between LTBI and DM-2 has implications on global TB control: a mathematical model forecast that it would not be possible to eliminate TB by the year 2035 if the incidence of DM-2 continues to increase worldwide (Pan et al., 2015). There is also evidence of a relationship between glucose control and the risk of LTBI, whereby an elevated glucose level (fasting blood glucose or HbA1c) is associated with an increased risk of developing LTBI (Martinez et al., 2017). What is not understood is the role of transient hyperglycemia in LTBI: in patients with active TB an association between transient hyperglycaemia and mortality and treatment failure has been demonstrated (Boillat-Blanco et al., 2016), but this has not been evaluated in populations with LTBI.

An accurate estimation of the prevalence of a disease relies on strong diagnostic methods. However, the diagnosis of LTBI is notoriously challenging. Moreover, the methods used to diagnose LTBI may be less effective in DM-2 patients: these methods are surrogate tests that infer the presence of LTBI based on the patient's immunological response to a stimulus, yet immune responses may be impaired in people with DM-2, thereby affecting the performance of these tests. The Tuberculosis Skin Test (TST) has been shown to have poorer sensitivity, and the Interferon-γ release assays (IGRAs) to have higher rates of false negatives, in patients with DM-2 than in non-diabetic patients (Faurholt-Jepsen et al., 2014).

In addition to the increased risk of LTBI in people with DM-2, these individuals have a higher risk (approximately 3-fold) of developing active TB (Jeon and Murray, 2008). DM-2 compromises an individual's immune system in such a way that favors TB reactivation. For example, adipocytokines (cytokines produced by adipose tissue) are associated with inflammatory processes in DM-2, where deregulation of adipocytokines may be related to the increased risk of TB among patients with DM-2 (Pavan Kumar et al., 2016).

There are no strong recommendations on whether or not to offer TB prophylaxis to people diagnosed with DM-2. Unlike other high-risk populations (e.g., HIV infected patients), LTBI prophylaxis and treatment in DM-2 have not been thoroughly evaluated; to the best of our knowledge, no specific trials have been performed to determine the effect of any therapy (e.g., isoniazid monotherapy or rifapentine plus isoniazid) on the risk of developing active TB in DM-2 patients. Further studies are also needed to investigate the "antibiotic" properties of DM-2 treatment and control. For example, there is some evidence that metformin, an oral drug used for glycaemic control, reduces the growth of *M. tuberculosis* in vitro (Singhal et al., 2014), and that achieving good glucose control may have a role in reducing the risk of patients with LTBI going on to develop active TB (Lee et al., 2016).

*Chronic kidney disease*

Patients with renal failure, specifically patients with chronic kidney disease (CKD) on dialysis, have a morbidity and mortality due to infections of about 50% and 20%, respectively. This is likely to be associated with alterations in the immune system due to uremia (Romanowski et al., 2016): changes in innate and adaptive immune responses occur in patients with CKD stage $\geq$3, worsening as the stage progresses, and in patients who are on immunosuppressive therapy following renal transplantation, which can lead to a state of uremic inflammation (Carrero and Stenvinkel, 2010).

The risk of acquiring LTBI or of developing active TB is high in patients with CKD because, apart from the immunity problems already described, comorbidities such as diabetes are common and these further increase this risk. Incidence of TB increases further with advancing stage of CKD: a study that included more than 8000 patients with CKD in the United Kingdom found an incidence of 126 cases of active TB per 100,000 patient-years (95% CI 97–169), and the incidence was lower in those patients with stage 1 CKD (92 per 100,000 patient-years) compared with those who received dialysis (257 per 100,000 patient-years) (Moran et al., 2018). Outcomes, including risk of death, are also worse among patients with TB who are on dialysis. Because of both the increased risk of TB and worse outcomes, it has been suggested that patients with CKD or on dialysis should be classified as a high risk group in need of interventions to prevent active TB.

Screening should be considered in all people with CKD Stages 4 or 5, and all those on hemodialysis, due to the deterioration in immunity with CKD progression leading to increasing risk of TB reactivation, and in all patients awaiting renal transplantation due to the immunosuppressive therapy required following this procedure. This should be performed using IGRA or TST, depending on the availability of the test. The TST is associated with rates of cutaneous anergy of 50% in CKD patients due to poor immune responses (Myall and Milburn, 2017). The effect of CKD on IGRA results is not known, however a recent cost-effectiveness analysis has shown IGRA to be both more cost-effective and associated with better outcomes than testing strategies employing TST in patients with CKD (Campbell et al., 2019). The WHO currently recommends either TST or IGRA for LTBI screening for these patients (WHO, 2018b).

*Rheumatoid arthritis*

The introduction of disease-modifying antirheumatic drugs (DMARDs) such as antitumor necrosis factor (anti-TNF) agents, which are effective for the management of RA and other inflammatory disorders, has been associated with TB reactivation in these patients (Cantini et al., 2017). RA patients using DMARDs have been shown to have a 4-fold increased risk of developing active TB in comparison to RA patients not receiving DMARDs, and this risk is increased to 17-fold compared to the general population (Ai et al., 2015). This is sufficient for all RA guidelines to include mandatory screening for LTBI and active TB in RA patients in whom DMARD therapy is being considered (WHO, 2018b; Singh et al., 2016). However, these guidelines do not recommend screening for LTBI in RA patients upon diagnosis, despite the evidence of an elevated risk in these patients compared to those without RA.

Unfortunately, as is the case for other non-communicable diseases (including DM-2 and CKD), there are no data guiding how to test for LTBI in RA patients specifically. One study reported that the agreement level between TST and IGRA was around 73% in RA patients (Pyo et al., 2018). As in DM-2 and CKD, the WHO and other academic institutions including the American College of Rheumatology recommend screening all RA patients for LTBI with either of these tests (WHO, 2018b; Singh et al., 2016).

No consensus been reached regarding prophylaxis for TB in RA patients. This is particularly relevant because of the risk of potential adverse events (i.e. hepatotoxicity) resulting from the use of isoniazid as a TB preventive therapy, and concerns about its safety in RA patients who are chronic consumers of several drugs such as methotrexate, NSAIDs, corticosteroids and other anti-inflammatory agents which have adverse effects of their own.

## Conclusions

The world population is facing a shifting of health problems. This is due to a combination of factors, such as a longer life expectancy and better healthcare including the development of new treatments and improved access to healthcare (i.e., universal health coverage). Nevertheless, in many regions of the world

infectious diseases such as TB are still highly prevalent. The control and elimination of these infections depend to a large extent on how they are managed among high-risk individuals. There is increasing evidence that people with non-communicable diseases constitute a high-risk group for both acquiring LTBI and developing active TB. Although there are clear pathophysiological and immunological pathways between several non-communicable diseases and LTBI and/or TB, further studies evaluating better screening tools for LTBI, safe prophylaxis, and treatments for TB are much needed in patients with DM-2, CKD and RA.

## Conflicts of interest

No competing interest declared.

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## Ethics

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## References

Ai JW, Zhang S, Ruan QL, Yu YQ, Zhang BY, Liu QH, et al. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-alpha antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. J Rheumatol 2015;42(12):2229–37.

Boillat-Blanco N, Ramaiya KL, Mganga M, Minja LT, Bovet P, Schindler C, et al. Transient hyperglycemia in patients with tuberculosis in Tanzania: implications for diabetes screening algorithms. J Infecti Dis 2016;213(7):1163–72.

Campbell JR, Johnston JC, Ronald LA, Sadatsafavi M, Balshaw RF, Cook VJ, et al. Screening for latent tuberculosis infection in migrants with CKD: a cost-effectiveness analysis. Am J Kidney Dis 2019;73(1):39–50.

Cantini F, Nannini C, Niccoli L, Petrone L, Ippolito G, Goletti D. Risk of tuberculosis reactivation in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis receiving non-anti-TNF-targeted biologics. Mediators Inflamm 2017;2017:8909834.

Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease—what have we learned in 10 years?. Semin Dial 2010;23(5):498–509.

Faurholt-Jepsen D, Aabye MG, Jensen AV, Range N, Praygod G, Jeremiah K, et al. Diabetes is associated with lower tuberculosis antigen-specific interferon gamma release in Tanzanian tuberculosis patients and non-tuberculosis controls. Scand J Infect Dis 2014;46(5):384–91.

Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008;5(7)e152.

Koesoemadinata RC, McAllister SM, Soetedjo NNM, Febni Ratnaningsih D, Ruslami R, Kerry S, et al. Latent TB infection and pulmonary TB disease among patients with diabetes mellitus in Bandung, Indonesia. Trans R Soc Trop Med Hyg 2017;111(2):81–9.

Lee PH, Fu H, Lai TC, Chiang CY, Chan CC, Lin HH. Glycemic control and the risk of tuberculosis: a cohort study. PLoS Med 2016;13(8)e1002072.

Lee MR, Huang YP, Kuo YT, Luo CH, Shih YJ, Shu CC, et al. Diabetes mellitus and latent tuberculosis infection: a systematic review and metaanalysis. Clin Infect Dis 2017;64(6):719–27.

Magee MJ, Salindri AD, Gujral UP, Auld SC, Bao J, Haw JS, et al. Convergence of non-communicable diseases and tuberculosis: a two-way street?. Int J Tuberc Lung Dis 2018;22(11):1258–68.

Martinez L, Zhu L, Castellanos ME, Liu Q, Chen C, Hallowell BD, et al. Glycemic control and the prevalence of tuberculosis infection: a population-based observational study. Clin Infect Dis 2017;65(12):2060–8.

Martinez-Aguilar G, Serrano CJ, Castaneda-Delgado JE, Macias-Segura N, Hernandez-Delgadillo N, Enciso-Moreno L, et al. Associated risk factors for latent tuberculosis infection in subjects with diabetes. Arch Med Res 2015;46(3):221–227.

Moran E, Baharani J, Dedicoat M, Robinson E, Smith G, Bhomra P, et al. Risk factors associated with the development of active tuberculosis among patients with advanced chronic kidney disease. J Infect 2018;77(4):291–5.

Myall K, Milburn HJ. An update on the management of latent tuberculosis infection and active disease in patients with chronic kidney disease. Pol Arch Intern Med 2017;127(10):681–6.

Pan SC, Ku CC, Kao D, Ezzati M, Fang CT, Lin HH. Effect of diabetes on tuberculosis control in 13 countries with high tuberculosis: a modelling study. Lancet Diabetes Endocrinol 2015;3(5):323–30.

Pavan Kumar N, Nair D, Banurekha VV, Dolla C, Kumaran P, Sridhar R, et al. Type 2 diabetes mellitus coincident with pulmonary or latent tuberculosis results in modulation of adipocytokines. Cytokine 2016;79:74–81.

Pyo J, Cho SK, Kim D, Sung YK. Systemic review: agreement between the latent tuberculosis screening tests among patients with rheumatic diseases. Korean J Intern Med 2018;33(6):1241–51.

Romanowski K, Clark EG, Levin A, Cook VJ, Johnston JC. Tuberculosis and chronic kidney disease: an emerging global syndemic. Kidney Int 2016;90(1):34–40.

Singh JA, Saag KG, Bridges Jr. SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol (Hoboken, NJ) 2016;68(1):1–26.

Singhal A, Jie L, Kumar P, Hong GS, Leow MK, Paleja B, et al. Metformin as adjunct antituberculosis therapy. Sci Transl Med 2014;6(263) 263ra159.

WHO. The end TB strategy: global strategy and targets for tuberculosis prevention, care and controlafter 2015. Geneva: World Health Organization; 2014 Available from: https://www.who.int/tb/post2015_strategy/en/.

WHO. Global tuberculosis report. World Health Organization; 2018 Available from: http://www.who.int/iris/handle/10665/274453.

WHO. Latent TB infection: updated and consolidated guidelines for programmatic management. World Health Organization; 2018 Available from: https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1.