

## EDITORIAL

### Suggestions for improving the co-existing tuberculosis and diabetes melitus in primary care



### Sugerencias para mejorar la coexistencia de tuberculosis y diabetes mellitus en atención primaria

#### Snapshot of the literature

Tuberculosis (TB) (a communicable) and diabetes mellitus (DM) (a non-communicable) disease have received a lot of attention in WHO and public health policies. However, they aren't seen together as a set of diseases that could potentially influence each other. As regards TB 10.4 million new cases of TB worldwide were reported in 2016<sup>2</sup> especially in LMIC and that's why WHO developed the "End TB Strategy", which intends to end TB by 2035, by broadening the diagnostic process and treatment and enhance management of TB risk factors.<sup>2</sup> Similarly, DM is very prevalent in the developed world and is considered one of the most important non communicable diseases; recognized as a major policy need by WHO.

The interdependence of these two diseases hasn't received a wide attention and still guidelines/guidance are monodisease oriented. However, DM is estimated to be the cause of 15% of present TB cases, mainly due to chronic hyperglycemia impairing the hosts defenses. Recent systematic reviews<sup>2-6</sup> of the literature have collected a wide range of studies indicating an association between the development of TB and diabetes mellitus (DM). Meta-analysis and systematic reviews suggest that DM increases the risk of developing TB from 1.5 to 4 folds and further escalates the severity of the disease and the outcome of the treatment<sup>2,3,7</sup>; posing a significant barrier for effective TB control programs. Moreover, patients with both diseases seem to have a higher risk of drug resistance or relapse of TB or death compared to those with TB alone.<sup>2</sup> Therefore, patients with diabetes should receive more attention for an early diagnosis of TB and management should be more individualized especially as patients with TB with concurrent diabetes tend to suffer from worse tuberculosis treatment outcomes.

The current opinion article summarizes the most prevalent evidence of the literature and expresses our perspectives on this "hot" topic; It's aim is to also

give some guidance for the daily primary care clinical practice.

### Raising the awareness of the community is the first step for reducing both the TB and DM prevalence in the community

PCPs are familiar with the importance of the risk factors assessment and control when operating in daily clinical practice. However, this is particularly true as regards their impact in the overall health of patients and as regards guidelines again risk factors assessment are monodisease oriented.<sup>1</sup> To be able to think more broadly is a challenge. For example, the attitude would be different if we consider that TB has several significant risk factors, which combined with DM can even quadruple the risk for TB. Namely, tobacco smoking, alcohol, and low BMI are amongst the most prominent risk factors for TB.<sup>4</sup> Furthermore, tobacco smoking is associated with more severe symptoms of TB and higher mortality rates. Smoking cessation is obviously a target for diabetes which posed the patient at high cardiovascular risk and TB. Usually as regards diabetes PCPs always suggest diet and lowering of the BMI, but they should be aware that BMI < 18.5 has been associated with increased risk for active TB. Therefore, GPs should strive to find a balance between managing DM and adjusting BMI.<sup>4</sup> Moreover, further research is needed to clarify the most optimal value for BMI and reduce the risk for both DM and TB.

### Bi-directional screening a possible solution to effectively prevent the emergence of either TB or/and DM

It is becoming evident that TB requires a holistic approach to be effectively prevented. HCPs should proactively try and control the risk factors associated with TB. An holistic approach means, that PCPs should take into account not only the disease but, also other factors such as comorbidities, emotional and socio-economic status which, may inhibit an otherwise effective prevention or treatment plan.<sup>3</sup>

Bi-directional screening for both TB and DM, seems to be the most effective strategy for preventing them, especially in high-risk individuals and countries with high prevalence of both diseases.<sup>3</sup> In these occasions, it could be proposed that as soon as a GP diagnoses either TB or DM screens

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also for the other disease, to promptly prevent, diagnose and treat. However, bi-directional screening can be costly and there's still a need for more research to prove its effectiveness.<sup>3</sup> Although, bi-directional screening would be the ideal case,<sup>8</sup> in terms of cost effectiveness it has been recommended to screen for DM in people diagnosed with TB in high income country settings (due to resources available and high DM prevalence and higher positive predictive value of the screening test) but not for low-income countries where resources should primarily be dedicated to detecting the index disease of TB (or DM) depending on local epidemiology and disease burden first.<sup>8</sup>

### Multi-dimensional holistic strategies should be utilized when treating both TB and DM

A number of reviews<sup>2,6</sup> have concluded that DM increases the risk of both treatment failure and death, death alone, or relapse among patients with TB. A comprehensive plan for managing TB and DM should be a priority, especially in Primary Health Care (PHC), with an emphasis on TB treatment in patients with DM. Such a plan may include adopting a healthier lifestyle, testing for suspected diabetes, improving glucose control, and increase clinical and therapeutic monitoring.

The most widely used strategy for controlling TB is the Directly Observed Therapy Short-Course (DOTS), which involves sputum smear analysis and chemotherapy. DOTS is quite effective for detecting and treating the disease. However, that might not be enough since, it has been suggested that people with uncontrolled blood glucose levels had significantly higher risk for active TB than those with controlled levels.<sup>2,4,6</sup> Therefore, clinicians should be aware that by specifically monitoring and controlling glucose in patients with DM, maybe important for preventing TB.<sup>2,4</sup> Another important aspect that deserves attention as depicted in a meta-analysis is the fact that people with DM are more prone in developing multi-drug resistant TB, therefore a more rigorous treatment and follow up is needed.<sup>9</sup>

### Metformin as a low-cost solution?

DM requires high quality of care, meaning constantly monitoring and making adjustments to treatment, to avoid high mortality rates.<sup>5</sup> Metformin is recommended as first choice in guidelines and is one of the most used and affordable drugs for DM. Despite, its glycemic controlling effects, it has been suggested as a medication with a possible beneficial role in effectively preventing and treating TB in patients with DM. This is due to its capacity to increase the isoniazid activation, the host's immune cells activity and reduce the deleterious inflammation.<sup>6</sup> Furthermore, a meta-analysis highlighted that metformin can lower the risk of TB and mortality of patients with DM.<sup>6</sup> Therefore, it is recommended that metformin is utilized in patients with DM, if there's high probability of TB infection and there aren't any reasons against its use.

## Conclusions

It is becoming increasingly evident that the ongoing and ever-growing DM epidemic is thwarting the "End TB Strategy" initiative.<sup>2</sup> Therefore, a new health strategy is required which raise awareness of the two diseases interconnection, to better prevent and manage them. To that direction primary care may have a leading role. Thus, researchers, GPs, clinicians, and policy makers should work together to bring forth a guidance with specific suggestions and measures to effectively win the battle against both TB and DM.

### Key messages

- TB remains one of the most prominent challenges for Primary health care with over 10.4 million cases globally.
- DM increases threefold the risk of developing TB, mainly because diabetes impairs host defense.
- General practitioners should focus not only on early diagnosis and effective treatment of TB but also in improving awareness and promoting prevention strategies to their communities.<sup>1</sup>
- By educating about the disease and by effectively managing the disease risk factors).
- Bi-directional screening for both TB and DM is strongly recommended since it allows for faster and more efficient treatment especially in countries where TB has a high prevalence.
- The role of PCPs in controlling glucose levels of patients with diabetes is crucial as this could reduce the risk of TB development.
- PCPs should include in their consultation with a patient with diabetes not only management issues but also investigate and proactively act as regards the tobacco, alcohol use, but also their increased BMI since all together they exponentially increase the risk for TB.
- Additionally, metformin a low cost first step treatment for DM decreases the risk for TB but also improves the immune response in individuals suffering from TB. Therefore, it is strongly recommended that GPs use it on DM patients at high risk of TB exposure.

### Ethical considerations

All authors declare no competing interest related to this article.

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## Conflict of interest

None.

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