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Tuberculosis and comorbidities: treatment challenges in patients with comorbid diabetes mellitus and depression

Guillermo Cáceres, Rodrigo Calderon and Cesar Ugarte-Gil

***Abstract*:** Tuberculosis is one of the leading causes of death worldwide, primarily affecting low- and middle income countries and individuals with limited-resources within fractured health care systems. Unfortunately, the COVID-19 pandemic has only served to aggravate the already existing diagnostic gap, decreasing the number of people who get diagnosed and thereby complete successful treatment. In addition to this, comorbidities act as an external component that when added to the TB management equation, renders it even more complex. Among the various comorbidities that interact with TB disease, diabetes mellitus and depression are two of the most prevalent among non-communicable diseases within the TB population and merits a thoughtful consideration when the healthcare system provides care for them. TB patients with diabetes mellitus (TB-DM) or depression both have an increased risk of mortality, relapse and recurrence. Both of these diseases when in presence of TB present a 'vicious-circle-like' mechanism, meaning that the effect of each disease can negatively add up, in a synergistic manner, complicating the patient's health state. Among TB-DM patients, high glucose blood levels can decrease the effectiveness of anti-tuberculosis drugs; however, higher doses of anti-tuberculous drugs could potentially decrease the effects of DM drugs. Among the TB-depression patients, not only do we have the adherence to treatment problems, but depression itself can biologically shift the immunological profile responsible for TB containment, and the other way around, TB itself can alter the hormonal balance of several neurotransmitters responsible for depression. In this paper, we review these and other important aspects such as the pharmacological interactions found in the treatment of TB-DM and TB-depression patients and the implication on TB care and pharmacological considerations.

Keywords: tuberculosis, diabetes, depression, therapy, comorbidities

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Correspondence to:
Cesar Ugarte-Gil
Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Av. Honorio Delgado 430–San Martin de Porres, Lima, Perú

School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Perú London

School of Hygiene and Tropical Medicine, 15102 London, UK
cesar.ugarte@upch.pe

Guillermo Cáceres
Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Perú

Rodrigo Calderon
Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Perú

School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Perú

Introduction

Tuberculosis (TB) is a communicable disease and a leading cause of death worldwide.[1] Before COVID-19 pandemic, TB was the main cause of death from a single infectious agent, even higher than HIV. This pandemic affected negatively the essential TB services, showing a substantial global decrease in the diagnostic stage of the TB care cascade, falling from 7.1 million in 2019 to 5.8 million in 2020 in the number of individuals with a newly TB diagnosis, this is an 18% decline that brings us back to the diagnostic rates of 2012.[1] Considering that roughly 10 million people developed TB in 2020, the diagnostic gap has widened substantially.[1]

In low- and middle- income countries (LMIC), TB is one of the main causes of significant mortality,[2] especially in patients with comorbidities. The most common and well-described comorbidities in TB cases are HIV infection, which correlation with TB is well established;[3] diabetes mellitus (DM), which threatens the continuing efforts to control TB;[4] alcohol abuse;[5] smoking;[6] depression, which has a negative impact in clinical manifestations and treatment adherence;[7] and

more recently reported as an emerging TB comorbidity, COPD.[8]

A strong relationship between TB, DM and depression has been established in multiple studies. The inflammation generated by the TB infection may increase the risk for depression. Meanwhile, depression may jeopardize host immunity, increasing the risk for TB infection. In addition, DM is also known to increase risk for TB; it is usually comorbid with depression, and it's co-occurrence could be due to its similar pathophysiological pathways.[9] Healthcare for patients with the comorbidities mentioned previously is complex and difficult to treat since the occurrence and progression of one condition can influence the other ones and vice versa.[10]

To achieve proper control of the disease, the rate of patients who reach a cured state must be no less than 85%, according to WHO.[11] The socioeconomic barriers, clinical characteristics, and resistance to anti-tuberculosis drugs are among the reasons for this objective not being accomplished yet. Multiple studies indicate that the presence of comorbidities in TB patients is associated with unfavorable outcomes of the TB treatment.[11] Therefore, the coexistence of certain non-communicable diseases with TB represent several health challenges, requiring a focus on multidisciplinary collaboration and integrated strategies, to accurately deal with this double burden of disease.[12]

The aim of this review is to discuss some of the most impactful challenges that patients with TB–DM and TB–depression face, in different settings, regarding the clinical presentation, diagnosis, and combined management of these conditions, exploring in more detail the multiple interactions between the drugs used in their treatment.

Tuberculosis and diabetes: twin epidemics

Epidemiology

A systematic review of 200 studies with more than 2 million people infected with active tuberculosis, showed a prevalence of DM in TB patients of 15.3%, with an estimated prevalence of 7.7% for Central and Latin America. Patients with DM have a three times risk of developing TB,[12,13] and by 2030, it is expected that DM patients will rise to 366 million, from an estimated 171 million for the year 2000, with three-quarters of them living in low-income countries.[14] These numbers are expected to go higher with the increasing worldwide rates of obesity[15] and even higher if we consider that 179 million individuals have not been diagnosed with DM yet.[16]

Diabetic patients have an elevated risk of TB negative outcomes such as: mortality, relapse (posterior episode of TB disease because of the reactivation of the original infecting strain of Mycobacterium tuberculosis (MTB))[17] and recurrence (diagnosis of a posterior episode of TB after the first TB episode has been clinically cured)[17]. All of whom contribute to the proportion of 10% to 25% among 1.5 million individuals who perish from TB every year that have comorbid DM as well.[18] DM care represents a big challenge to LMIC, where TB has a high prevalence and mortality rates. Under these circumstances, comorbidities such as DM can complicate TB care and control even further, making it difficult for the public health services to manage these overlapping diseases.[14]

Immunology

It's unknown the exact biological mechanism that links these two diseases. Several authors agree that immunity is altered in diabetic patients in many levels, such as a depressed polymorphonuclear leukocyte function, an affected leukocyte adherence, chemotaxis, and phagocytosis.[19] Cellular innate immunity dysregulation coupled with an increased glucose concentration environment contributes to the larger prevalence of the TB infection.[18] Hyperglycemia has been assumed to favor the growth and propagation of MTB,[20] thus improving glucose control may overturn the harm caused to the immunological balance and diminish the vulnerability to the infectious agent.[18]

As shown, TB exerts its effects complicating the glycemic control and the severity of infections in DM patients,[14] such as skin, gastrointestinal, respiratory, and urinary tract infections, among others; the latter being caused by the reduction in the phagocytic activity.[21]

The state in which the MTB stays in the host's immune system without clinical manifestations and radiological findings of active TB disease, is called latent tuberculosis infection (LTBI).[17] Out

of the small quantity of studies that have assessed the prevalence of LTBI in DM patients, reported rates range from 28.2% to 42.4%.[22] In DM patients, the risk of LTBI is increased, and the risk of progression to active TB is also increased.[23] The immunological hypothesis that may explain the DM and LTBI relationship is based on the glycation of CD271 domain of mesenchymal stem cells in uncontrolled DM patients, which may change it's lifespan, becoming a potential niche for MTB in LTBI.[23]

Severity of disease. Concurrence of TB and DM can vary or even worsen the clinical manifestations of the disease. Clinically, TB–DM patients may have worse symptom presentation compared to non TB-DM, including increased weight loss, dyspnea, sweats, and prolonged fever duration.[16] In addition, they have a more severe lung involvement, X-ray evidence show that TB-DM patients have more parenchymal lesions and cavities,[24,25] and CT scans have shown bilateral pulmonary involvement and advanced extensive pulmonary lesions affecting all lobes, findings that correlate with baseline clinical severity and response to treatment.[26] These findings are in accordance with a higher bacillary burden at presentation in diabetic patients[17] and a delay to both sputum smear and culture conversion time.[18] These characteristics could aggravate if the TB-DM patient has poor glycemic control.[27–30] Regarding the frequency of extrapulmonary involvement in TB-DM patients, evidence shows that TB-DM patients have a lower risk of developing extrapulmonary presentation.[31–33]

Also, the TB-DM patients are at a higher risk (two-fold) of TB drug resistance, this has been suggested in a previous meta-analysis with several studies included ($n = 19$).[34] Some specific mutations found in TB-DM patients conferred resistance to isoniazid, ethionamide, fluoroquinolone, and rifampicin.[35] The drug resistance found was independently associated with the DM glycemic control. A contributor for the resistance development might be the lower concentrations of TB drugs found in TB-DM patients.[36,37]

All these findings regarding the severity of the clinical presentation translates into adverse treatment outcomes in TB-DM patients, such as an increased risk in delay in mycobacterial clearance, treatment failure, death, relapse, re-infection, and drug resistance.[34,38,39] A 2011 meta-analysis that included four studies that controlled potential confounders found a nearly five-fold mortality risk in TB-DM patients compared to non TB-DM.[40] However, an updated 2019 meta-analysis that included 64 studies found a nearly two-fold mortality risk for TB-DM vs TB-only patients.[34]

Diagnostic and management challenges. There are several challenges that impacts the diagnosis of both diseases, especially in high burden populations. A variable clinical presentation, which TB–DM patients present, may delay the diagnosis or not diagnose the presence of either of the diseases.[35] In LMIC, the absence of diagnostic tools and difficult access to medical care, may also delay the confirmation of TB or DM, and have outcome repercussions.[35] To overcome this, a main recommendation from the Collaborative Framework for Care and Control of Diabetes is to screen for DM in patients with diagnosed TB, and screen for TB in DM patients from countries with high prevalence of TB.[36]

The tuberculin skin test (TST), is the most common diagnostic method for LTBI. It works by injecting purified protein derivative (PPD) intradermally in the forearm, evaluating the presence of an induration in the following 48 to 72 hours.[35] However, in TB–DM patients, the multiple immunological deficiencies may increase the current cut-off value, making this diagnostic test less sensitive in comparison with patients with no DM.[37] The interferon-gamma release assay (IGRA), is an immunological test that measures interferon gamma (IFN-γ) release by T cells, in exposure to determined MTB antigens, and may be helpful in the diagnosis of LTBI.[38] Nonetheless, indeterminate IGRA results may be related with immunosuppression, being this a possible scenario for TB patients with comorbid DM, which could develop immunological dysregulations.[38,39]

New diagnostic methods for TB have been developed, such as the Urinary TB LAM or Xpert MTB/RIF assay, having more advantages than out-dated diagnostic tools. The urinary TB LAM is a urine test that detects the lipoarabinomannan (LAM) antigen, which is a glycolipid released by metabolically active bacilli.[40] This diagnostic tool has a low cost, is rapid and easy to apply, and very useful among TB patients with comorbid HIV and very low CD4 + cells count.[41,42] In TB-DM patients, the effect of glycosuria on the urinary TB LAM test has not been evaluated yet.

However, reports suggest that the MTB cell wall polysaccharide composition may change in TB-DM patients, which could alter the test sensitivity, due to the lower levels of urinary LAM concentration caused by glycosuria.[43]

On the other hand, molecular testing, such as nucleic acid amplification tests (NAATs) for the diagnosis of TB, has been recommended by the WHO, due to its ability to detect MTB plus rifampicin and isoniazid susceptibility, faster than smear microscopy and mycobacterial culture.[44,45] These NAATs endorsed by WHO include line probe assays (LPA), loop-mediated isothermal amplification (LAMP), Xpert MTB/RIF, and Truenat MTB.[45] The Xpert MTB/RIF works with a sputum sample, which is mixed with the assay's reagent, and then placed in a cartridge that is processed in the GeneXpert machine system.[46] Even though this diagnostic tool could be expensive, is convenient due to its capability of rapid TB diagnosis and detection of rifampicin and isoniazid susceptibility, especially in cases with high suspicion of TB infection and difficult diagnosis, which is common in TB–DM patients.[35,47]

According to WHO, TB–DM patients should have an integrated and interdisciplinary co-management to reduce the burden of disease.[48] However, the best management and treatment strategy is still under research and remains unknown.

An important challenge in the management of TB-DM patients is medication adherence. Interruption of medication intake by the patient can happen for multiple reasons. One of them is experiencing adverse effects from the combination of TB and DM drugs, the most frequent being itching, dizziness, and vomiting.[49] As an example, TB-DM patients on metformin with rifampicin experience a higher incidence of gastrointestinal adverse (nausea and vomiting) effects compared to metformin alone, needing additional guidance such as: taking the medications in separated times, with food, and possibly metoclopramide.[50] In addition to the medication's adverse effects, the prior perception of the pill burden of taking too many medications is another important reason for abandoning treatment, underscoring the need to consider the patient's belief and knowledge of their condition.[50,51]

Therefore, even though DOT is a successful strategy for monitoring TB treatment adherence, patients can stop taking their DM medications, and in many cases, without informing their treating physicians. Moreover, the situation gets worse as TB clinics often do not monitor DM blood markers through finger prick glucose testing or H1Abc blood levels, thereby not having the chance to detect uncontrolled DM in patients.[50] Given that it is known that DM comorbid condition is a risk factor for various negative TB outcomes, TB clinics should offer differentiated care for this type of patients,[51,52] as it is feasible to manage uncontrolled DM if detected early in TB treatment. All this highlights the importance of monitoring, educating, and counseling when dealing with medication adherence in TB-DM patients.

Another main challenge for TB–DM patients, according to multiple studies, is treatment failure. This could be due to poor glucose control, as chronic hyperglycemia reduces the efficiency of the antituberculosis treatment and affects the elimination of MTB by compromising the microvasculature and decreasing the perfusion in the lungs for optimal immune surveillance. As a second reason, a deficient plasma level of antituberculous drugs in DM patients versus non-DM patients has been observed, and using a therapeutic drug-monitoring intervention or establishing a corrected dose, especially with uncontrolled DM patients, might be necessary for effective treatment.[31,53,54]

Ideally, every TB-DM patient should complete the entire length of the TB treatment, while also managing DM with diet, lifestyle modifications, metformin, insulin, or any other drug used for TB–DM patients, avoiding possible interactions with TB drugs.[18] For this reason, is important to pay attention to each component of the care cascade process, from the engagement of the patient up to the medications prescribed for every individual case.

Engagement of TB–DM patients with the health system, particularly in the early stages of the TB treatment, represents an opportunity for counseling on lifestyle interventions such as nutrition, weight loss, smoking cessation, and physical activity. These patients should be assessed by interdisciplinary specialists such as an endocrinologist to confirm the DM diagnosis and give counseling on nutrition and lifestyle changes.[51]

Overlapping toxicities with the different types of drugs must be considered when the physician is

co-managing patients with TB and DM (Table 1).[14] Rifampicin, a cornerstone drug in the TB treatment, works by inhibiting bacterial RNA polymerase, blocking the path of the elongating RNA.[55]

Rifampicin induces various enzymes responsible for metabolizing multiple drugs (Table 3). It promotes the expression of cytochrome P450 (CYP) 3A4 both in the liver and intestine, reducing the plasma concentrations and effects of many CYP3A4 substrates.[55] It also induces CYP2 C and thus decreases the plasma concentrations of some drugs such as (*S*)-warfarin and first and second-generation sulfonylurea antidiabetic drugs such as: tolbutamide (1st generation) and glyburide, glimepiride and glipizide (2nd generation).[55]

Studies show that rifampicin reduces glyburide's plasma concentrations, C_{max}, and mean $t_{1/2}$ by 39%, 22%, and 17% respectively.[56] Similar outcomes were seen for glimepiride[57] and glipizide,[56] with a decrease in plasma concentrations of 34% and 22%, respectively. Consequently, glyburide's effect of controlling blood glucose levels was reduced by rifampicin. Blood glucose of TB–DM patients treated with sulfonylureas should be monitored when concomitant with a rifampicin treatment, and be careful if rifampicin treatment is withdrawn, in order to avoid any hypoglycemic episode. If necessary, the sulfonylurea dosage should be adjusted accordingly.[55]

Thiazolidinediones, a class of antidiabetic drugs, acts by binding to peroxisome proliferator–activated receptors, and they are often used as substrates for the cytochrome P450 enzymes. Rosiglitazone, a new oral antidiabetic thiazolidinedione, reduce it's mean plasma concentration by 66% and its C_{max} to 31% when given with rifampicin.[58] In a similar way, Pioglitazone, a thiazolidinedione compound used in the treatment of DM, showed a decrease of 54% in its plasma concentration from 3 hours onwards after ingestion.[59] Similar to sulfonylurea antidiabetic drugs, this could result in poor glycemic control, so the physician in charge must supervise patients treated with thiazolidinediones, adjust dosages if necessary, and decrease dosages if treatment is discontinued.

The meglitinide class of antidiabetic drugs, such as repaglinide and nateglinide, act reducing blood glucose concentration by enhancing insulin secretion from the pancreas.[55] Repaglinide's mean absolute bioavailability is around 60%, and is metabolized mainly by CYP3A4 in the liver. Studies show that rifampicin reduced the AUC of repaglinide by 57%, reducing its blood glucose lowering effect.[60] Nateglinide is a short-acting antidiabetic drug, and in-vitro studies has shown that cytochromes P450 (CYP) 2 C9 and 3A4 play a part in nateglinide metabolism, therefore is affected by rifampicin, decreasing its mean AUC of plasma concentration by 24%.[61] Thus, a close monitoring of blood glucose concentrations and dose adjustments of these antidiabetics must be ensured when administered in combination with rifampicin, and especially if rifampicin is discontinued.[55]

Compared to the previous DM medications, the biguanide antidiabetic drug, metformin, is a good alternative, as it is not metabolized in the liver. Furthermore, multiple studies report that metformin can be beneficial as an adjunct to antituberculosis therapy, due to reducing the mycobacterial growth by mitochondrial reactive oxygen species (ROS) production, enhancing the efficacy of anti-TB drugs like isoniazid, contributing to the infection control with the increase of the CD8 + T cells and CD4 + T cells in the lungs,[62] and reducing the excess of inflammation and lung tissue injury.[63] A reduction in TB incidence and mortality has also been reported in DM patients that use metformin.[64] In addition, metformin has been proposed as a potential host-directed therapy for TB, in view of its anti-inflammatory and immune strengthening properties.[65]

Lactic acidosis and gastrointestinal symptoms are among the main adverse effects of metformin, being some of the most relevant disadvantages of that drug.[50] And although there has been reports of a pharmacokinetic interaction with metformin and rifampicin (metformin receptors in the small intestine have been shown to be upregulated by rifampicin, resulting in increased absorption), this was not associated with a clinical or a modification in the metformin effect on glucose blood levels.[50]

Another main anti-tuberculous drug is isoniazid, which works inhibiting the cell wall lipid synthesis, by consuming nucleic acid pools and causing metabolic depression through peroxidative activation of the mycobacterial enzyme KatG.[66] It is well known that peripheral neuropathy is an adverse effect caused by treatment with isoniazid, thus pyridoxine should be given with isoniazid during TB treatment in diabetic patients.[14]

Table 1. Interactions between antituberculous drugs and DM medications or DM patients.

Antituberculous drug	DM medications / DM patients		Interactions	References
Rifampicin	1st generation sulfonylurea	Tolbutamide	Rifampicin promotes the expression of cytochrome P450 (CYP) 2 C9, reducing its plasma concentrations.	Niemi *et al*.[55]
	2nd generation sulfonylurea	Glibenclamide	Rifampicin promotes the expression of cytochrome P450 (CYP) 2 C9, reducing 39% of its plasma concentrations.	Niemi *et al*.[56]
		Glimepiride	Rifampicin promotes the expression of cytochrome P450 (CYP) 2 C9, reducing 34% of its plasma concentrations.	Niemi *et al*.[57]
		Glipizide	Rifampicin promotes the expression of cytochrome P450 (CYP) 2 C9, reducing 22% of its plasma concentrations.	Niemi *et al*.[56]
	Thiazolidinediones	Rosiglitazone	Rifampicin promotes the expression of cytochrome P450 (CYP) 2 C8, reducing rosiglitazone's mean area under the plasma concentration–time curve by 65%.	Park *et al*.[58]
		Pioglitazone	Rifampicin promotes the expression of cytochrome P450 (CYP) 2 C8, reducing pioglitazone's mean area under the plasma concentration–time curve by 54%.	Jaakkola *et al*.[59]
	Meglitinide	Repaglinide	Rifampicin promotes the expression of cytochrome P450 (CYP) 3A4, reducing repaglinide's mean area under the plasma concentration–time curve by 57%.	Niemi *et al*.[60]
		Nateglinide	Rifampicin promotes the expression of cytochrome P450 (CYP) 3A4 and 2 C9, reducing nateglinide's mean area under the plasma concentration–time curve by 24%.	Niemi *et al*.[61]
	Biguanide	Metformin	Rifampicin induced upregulation of metformin intestinal transporters, increasing its absorption. This was not associated with any clinically relevant or statistically significant increase in the glucose-lowering effect of metformin.	Te Brake *et al*.[50]
Isoniazid	DM patient		Isoniazid used in combination with rifampicin has also been associated with an increased risk of hepatotoxicity. TB–DM patients have been shown to have 50% less of the plasma concentrations of isoniazid and rifampicin than non-diabetic TB patients.	Mtabho *et al*.,[53] Dekkers *et al*.,[54] Niemi *et al*.,[55] Babalik *et al*.[67]
Pyrazinamide	DM patient		DM patients with a higher HbA1c increased the risk of not achieving therapeutic targets for pyrazinamide, due to increased levels of xanthine oxidase.	Kuppusamy *et al*.,[68] Alfarisi *et al*.[69]
Ethambutol	DM patient		In TB–DM patients with reduced kidney function, a dosage decrease is required. Neuritis optica should be suspected particularly in patients with complicated diabetes.	Riza *et al*.[51]

CYP, cytochrome; DM, diabetes mellitus; TB, Tuberculosis.

Isoniazid, which is often used in combination with rifampicin as part of the TB treatment regime, is associated with an elevated risk of hepatotoxicity, particularly in slow acetylators.[55] Furthermore, TB–DM patients have been shown to have 50% less of the plasma concentrations of isoniazid and rifampicin that non-diabetic TB patients have, and this merits a thorough consideration in how we standardize treatment for TB-DM patients.[53,54,67]

Pyrazinamide, a main anti-tuberculous drug in TB treatment, is converted by deamidase into pyrazinoic acid, which is the active metabolite responsible for stopping the growth of MTB. A study has shown that DM patients with an increased HbA1c had a higher risk of failing to reach the therapeutic levels needed for pyrazinamide. The main hypothesized reason was that pyrazinoic acid can get metabolized to 5-hydroxypyrazinoic acid 5-OH-POA by xanthine oxidase, and this enzyme is increased in plasma and hepatic levels of patients with DM and is also associated with HbA1c levels.[68,69] As a result, using this drug in patients with uncontrolled DM, may require an increase in its dosage. However, further research must be done in order to explore its association with clinical outcomes.[69]

Ethambutol, also forms part of the first-line anti-tuberculosis drugs, and works by inhibiting arabinosyl transferases which are involved in cell-wall biosynthesis.[70] Physicians must be cautious with patients who receive ethambutol and have a reduced kidney function, usually a decrease in its dosage is required. Neuritis optica, a well-known adverse effect of ethambutol, should be suspected in patients with complicated DM.[51]

Other anti-tuberculous drugs are on its way to be approved and ready to be used in the TB treatment regime, such as bedaquiline, pretomanid, delamanid, and fluoroquinolones. Bedaquiline is the only drug from the list that is metabolized by cytochrome P450, and if used in combination with rifampicin, a dose adjustment should be considered to reach therapeutic levels.[71] Delamanid, pretomanid and moxifloxacin are not metabolized by cytochrome P450.[72] Further research is required to be done in order to discover and understand the possible interactions of these new drugs.

Regarding their role in TB-DM patients, bedaquiline and delamanid are drugs whose effect depends on their blood concentration, as such, there has been concern for these relatively new drugs for treating MDR-TB among DM patients, given that they share multiple biochemical metabolic pathways.[73] Animal models in rats have shown that bedaquiline blood concentrations are altered in the presence of DM, making a dose adjustment necessary to avoid therapeutic failure.[73,74] However, recent evidence from 2021 that compares bedaquiline treatment in TB patients vs TB-DM patients has shown that administering the same dose for both groups results in similar TB outcomes.[75] Similar studies need to be conducted for pretomanid. In the case of fluoroquinolones, although some agents have shown to alter metformin uptake in vitro,[76] or dysglycemia in general,[77] there is also a need for additional studies that focus specifically on TB-DM patients. On this second-line drugs, we can observe that more studies should be conducted in order to replicate these findings and have solid evidence for MDR-TB-DM patients' treatment

As shown, TB drug treatment affects DM treatment and vice versa. We have seen that DM, –especially poorly controlled DM– might benefit from a higher dosage of anti-tuberculosis drugs to reach effective concentrations. However, with higher doses of anti-tuberculosis drugs, we could potentially see a decrease in the effects of DM drugs. This phenomenon makes the health care of TB-DM complex and renders it to be in need of fine-tuned medications regime per case.

The TB-depression syndemic

Epidemiology

TB is commonly associated with depression, which is a significant psychiatric condition projected to be one of the most weakening health disorders by 2030.[78] TB and depression concurrence negatively affect adherence to TB treatment and increases mortality, thereby leading to an increased risk for drug resistance and community exposure to TB, demonstrating a bidirectional association.[9] Considering that TB is expected to have a big growth in the following years, it is necessary to ponder over its relevant association when establishing a treatment strategy.

Furthermore, depressed patients with TB might not pursue care, and even if they get to initiate medication, they tend be inconsistent with treatment regimen and completing it. Due to this, some authors hypothesize that depression would represent an undercovered responsible for the TB and MDR-TB rise.[79] Regarding TB treatment outcomes, death and loss to follow-up, has been significantly associated with depressive symptoms.[80]

Depression prevalence in individuals that have initiated TB treatment go from 11.3% to 80.2%, with a mean prevalence of 48.9% (95% CI: 48.3%-49.6%).[79] The prevalence of depression in TB patients is 3 times larger or more, compared to patients in good health.[78] In addition, TB may disproportionately affect populations from limited-resources environments with a small number of mental health specialists, making it harder to control the spread of infection.[79]

Expanding our comprehension of the interrelation between these disorders would help to improve TB clinical care and prevention in patients with depression, being especially helpful for LMIC, in which both diseases are in constant growth.[78]

The tuberculosis-depression syndemic model

Multiple authors are reframing the TB and depression comorbidity, as an complicated web of synergistic association between multiple biological, social, and behavioral factors.[81] In the biological aspect of it, the release of several hormones like glucocorticoids and opioids during chronic stress and depression may shift Th1 cellular immunity to a Th2 immune response (humoral immunity).[82] This shift has been shown to potentially lead to TB reactivation, loss of TB containment in granulomas and spread of MTB in the body.[81] In addition, TB may activate the expression of several pro-inflammatory cytokines, stimulating the generation of quinolinic and kynurenic acid, which acts by lowering the production of serotonin, dopamine, and norepinephrine, leading to depression and neurodegeneration.[83] As a consequence, biological effects from both diseases end up negatively affecting the individual synergistically.

In the social regard, the stigma associated with TB patients contributes to depression, leading to autonomic and neuroendocrine responses that soars the risk for depression and weakens the immune system.[81] The negative attitudes and behaviors regarding TB patients, could cause shame and guilt, promoting discrimination and social isolation, resulting in depression.[84]

Due to this, negative behavioral outcomes are expected in patients with TB and depression, such as alcohol and drug abuse,[85] exacerbating poverty, undernutrition, and immunosuppression. This behavior has also been associated with TB reactivation, delays in pursuing treatment, deficient adherence, re-infection,[86] loss to follow-up, and mortality.[81]

These 3 components (biological, social, and behavioral) remark the strong relation between TB and depression, and shapes the TB–depression syndemics. This new view is essential for recognizing the psychosocial needs of individuals with TB, and help health services to find an appropriate way to give integrated patient care.

Main risk factors and diagnostic challenges

One of the main challenges in patients with TB and depression, is that depression could be undiagnosed very often. In these patients, a depressed mood may be overlooked with being sick or poor, and not be recognized as a treatable condition. In addition, some TB symptoms may resemble depression, like low appetite, fatigue, irritability, and loss of interest in social environment, among others, which can lead to a missed diagnosis of comorbid depression.[81]

Another barrier is that it may be difficult for non-mental health specialists to distinguish between situational distress and clinical depression. In settings where few treatment options are available, health workers may be unwilling to ask patients about their mental health, even if a psychiatric disorder is evident.[81] Health workers should be able to distinguish specific symptoms of depression like melancholy and anhedonia, and symptoms that overlap with those of TB, like fatigue.[9]

The risk factors for depressive symptoms in TB vary by: age, patient demographics and modifiable lifestyle factors; these include marital status, dyspnea and other symptoms of pulmonary TB or chronic respiratory diseases, social stigma in recently diagnosed TB, low income, and smoking history.[78]

Some studies about TB and depression patients, ensure that health workers among resource-limited countries are often not aware of the depression and other psychiatric comorbidities. An interdisciplinary alliance between specialists in the mentioned fields would be ideal for a prompt detection and treatment of TB–depression patients. This could represent an opportunity for medical professionals, to aim for a faster detection and better care of psychiatric comorbidities, leading to superior clinical outcomes for TB.[81]

Management challenges

Evidently, TB–depression patients have shown to complicate the clinical care of both diseases, as they can affect one to each other and alter its clinical course. However, mental health disorders are not adequately addressed in TB national programs, and for this reason, more patient centered or differentiated care services are needed to not only provide the diagnosis and medication information, but to educate the patient and its social support at a psychological level about the inherent relationship between TB and mental health disorders and the challenges they might face and provide skills on how to overcome it or how to receive support.[87] Multiple psychological interventions have shown improvement in adherence to TB medication when depression was better managed in TB programs.[7,88,89] Also, interventions like social protection and healthcare services with comprehensive nursing would help to improve mental health and recovery in TB–depression patients.[78] This should help to reduce the increased mortality observed in this comorbid condition.[90]

Multiple factors could lead to a non-adherence to TB treatment. Factors regarding health systems and society (barriers to access mental health care, the limited awareness and stigma around TB patients), treatment (lack of resources, lack of guidelines for patient education and poor communication between diagnostic and treatment clinics), medical teams (lack of mental health professionals, limited time for patient education), and patient (poverty, drug use, large distances from home to treatment center, and poor understanding of the need to continue treatment after symptoms resolution) have been cited as reasons for TB treatment default.[91]

The Directly Observed Therapy (DOT) program, a five-element strategy used in the management of TB, which includes a direct observation of the treatment administration, has been recommended by the WHO since 1993, as one of the most effective ways to treat TB and improve the treatment adherence rates.[92] However, patient nonadherence to DOT still occurs, and the presence of psychiatric pathologies is partially responsible for it. Some evidence even proposes that DOT does not resolve the lack of treatment adherence in TB patients,[93] and suggests that patient-centered care would be the most recommended way to diminish the health system barriers, and contribute to TB eradication.[94] Also, several studies suggest the inclusion of mental health services in healthcare programs to provide psychiatric assessment before initiating TB treatment, intervention and reduction of the default rate in TB programs.[7]

A collaborative care model could be a cost-efficient strategy to integrate to the TB–depression control program.[78] Defined as a team-based intervention for care delivery by improving coordination of patient care. This model has had good results in boosting the control of medical diseases such as DM and coronary heart disease as well as improving depression symptoms, treatment adherence, and wellbeing.[95]

In addition, TB–depression patients have many pharmacologic interactions (Table 2), particularly isoniazid and rifampicin (Table 3), with various psychiatric medications.[7] Common metabolic pathways is the reason why many antidepressants and psychotropics may decrease the bioavailability of antituberculosis drugs, or the other way around.[96]

Tricyclic antidepressants, like nortriptyline, have pharmacokinetic interactions that may influence the effect of the antidepressant therapy in patients treated with many non psychotropic drugs.[97] Rifampicin has been described to interact with nortriptyline, decreasing its blood levels, thereby creating the need for larger doses during treatment phase, because of rifampicin's inducing effect on cytochrome P-450 oxidative enzymes.[98]

Sertraline is a universally consumed selective serotonin reuptake inhibitor (SSRI) used in depression and anxiety disorders treatment. Its Inhibitory effect on the cytochrome (CYP) P450 system is strongly established, as well as rifampicin and its powerful inducer effect of the CYP450 system.[99] A case report of coadministration of sertraline and rifampicin has shown a decrease in

Table 2. Interactions between antituberculous drugs and Depression medications or depressed patients.

Antituberculous drug	Depression medications / depressed patients		Interactions	References
Rifampicin	Tricyclic antidepressant	Nortriptyline	Rifampicin is a potent inducer of many CYP450 enzymes. Interacting with nortryptiline, reducing its serum levels and requiring higher.	Doherty *et al*.[98]
	SSRI	Sertraline	A case report of coadministration of sertraline and rifampicin, where sertraline showed a decrease in substrate plasma concentrations and therapeutic failure due to rifampin induction of cytochrome (CYP) P450 system.	Markowitz and DeVane[99]
		Vortioxetine	A study shows that rifampicin decreases vortioxetine's Cmax by 51% and AUC (area under a curve) by 72-77%	Chen *et al*.[101]
	Atypical antidepressant	Bupropion	Theoretically, rifampicin induction of CYP2B6 should augment bupropion metabolism, but further research needs to be done to fully support this view.	Chen and Raymond[103]
Isoniazid	Phenytoin & Diazepam		The inhibitory activity of isoniazid is associated with the usage of anticonvulsants, phenytoin, and carbamazepine. Isoniazid increases concentrations of benzodiazepines metabolized by oxidation, such as diazepam and triazolam. The combined effects of rifampicin and isoniazid is a decrease in the concentrations of drugs such as phenytoin and diazepam.	Doherty *et al*.[98]
	SSRI	Paroxetine	Paroxetine is metabolized by CYP2D6, which is minimally affected by isoniazid. Consequently, the potential drug interactions are not significant.	Trenton and Currier[105]
		Sertraline	Further research must be done in order to clarify whether sertraline inhibits CYP3A, which is implicated in the metabolism of isoniazid.	Trenton and Currier[105]
		Citalopram	Citalopram is metabolized principally by CYP2C19 and CYP3A4, being these last two enzymes inhibited by isoniazid.	Preskorn[106]
		Fluvoxamine	Fluvoxamine inhibits CYP1A2, CYP2C19, and possibly CYP3A3/4, all of which are inhibited by isoniazid as well.	Preskorn[106]
Linezolid	SSRI		Linezolid has mild MAOI properties and may cause serotonin syndrome when combined with SSRIs such as citalopram, escitalopram, sertraline, fluoxetine, paroxetine, venlafaxine, and duloxetine. Linezolid has also been associated with serotonin syndrome in patients on multiple antidepressants.	Sweetland *et al*.,[81] Doherty *et al*.[98]

CYP, cytochrome; SSRI, selective serotonin reuptake inhibitor.

substrate plasma concentrations and therapeutic failure of sertraline, due to rifampin induction of their metabolism.[99]

Vortioxetine works at several serotonin receptors, and many of them are still being studied.[100] Similarly, studies indicate that rifampicin reduces vortioxetine's Cmax by 51% and AUC by 72%-77%.[101] Therefore, increasing the dose might be needed when vortioxetine is co administered with, for example, rifampicin, a CYP450 inducer.

Bupropion is another drug used for depression that works by inhibiting the reuptake of dopamine and noradrenaline, and is metabolized by CYP2B6.[102] Theoretically, rifampicin induction of CYP2B6 should augment bupropion metabolism, but further research needs to be done to

Table 3. Drugs affected by rifampicin through CYP450 enzymes.[103]

	CYP1A2	CYP2B6	CYP2C9	CYP2C19	CYP3A4
CNS drugs central nervous system	Amitriptyline Bupropion Clomipramine Clozapine	–	Amitriptyline Clomipramine	Amitriptyline Clomipramine Phenytoin Clozapine	Amitriptyline Buspirone Clomipramine Zolpidem
Hypoglycemics	–	Pioglitazone	Glibenclamide Glipizide Nateglinide Rosiglitazone Tolbutamide	Repaglinide	Pioglitazone
HIV Antivirals	–	Efavirenz	Nelfinavir	Nelfinavir	Amprenavir Delavirdine Indinavir Nelfinavir Nevirapine Ritonavir Saquinavir
Benzodiazepines	–	–	–	–	Alprazolam Diazepam Midazolam Triazolam

fully support this view,[103] and the increased dosage of bupropion should be evaluated if needed.

Isoniazid is, to some extent, a strong inhibitor of various cytochrome P450 isozymes, and coupled with its role as a minor MAOI, it may interact with some antidepressant medications.[104] The coadministration of SSRIs or tricyclic antidepressants with MAOIs is contraindicated, as it could produce a serotonin syndrome,[98] causing symptoms ranging from mild agitation to high fever, seizures, and unconsciousness.[81]

Hepatic cytochrome P450 enzymes are in charge, to a large extent, for the metabolism of multiple drugs, like isoniazid, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. CYP2E1, CYP1A2, CYP2 C9, CYP2C19, and CYP3A isoenzymes are inhibited on different levels by isoniazid, slowing the metabolization of concurrent medications. All SSRIs might be processed by cytochrome P450 enzymes; however, the interactions of every medication varies, and literature points out that certain SSRIs may be a preferable alternative for concomitant treatment.[7]

Isoniazid can alter concentrations of specific drugs reaching toxic levels, due to its inhibitory effects. The usage of anticonvulsants, phenytoin, and carbamazepine, are among the main examples. Isoniazid also alters concentrations of benzodiazepines, like diazepam and triazolam. However, literature demonstrates that the general result of the combined effects of rifampicin (inductive effect) and isoniazid (inhibitory effect) result in a concentration reduction of drugs like phenytoin and diazepam.[98]

According to literature, paroxetine might be the most innocuous SSRI to co-administer with isoniazid. It is metabolized by CYP2D6, and the latter is minimally altered by isoniazid. Consequently, the medications interactions are not significant. Sertraline could be an alternate choice; however, further research must be done in order to clarify whether it inhibits CYP3A, involved in the biochemical metabolic pathway of isoniazid.[105]

Fluoxetine does not have a common metabolic pathway with isoniazid; nonetheless, its metabolite norfluoxetine inhibits CYP3A3/4, which has a half-life of up to 15 days, which is much longer than many other SSRIs. Due to this larger time, it has an increased potential for drug interactions.[106]

Citalopram is metabolized principally by CYP2C19 and CYP3A4, being these last two enzymes inhibited by isoniazid. Fluvoxamine

inhibits CYP1A2, CYP2C19, and CYP3A3/4, all inhibited by isoniazid as well. Consequently, one should consider an alternative drug before choosing isoniazid.[106]

Linezolid, an oxazolidinone drug and antibiotic used mainly as part of MDR-TB treatment regime, also has mild MAOI properties and may cause serotonin syndrome[81] when combined with SSRIs such as citalopram, escitalopram, sertraline, fluoxetine, paroxetine, venlafaxine, duloxetine, and in individuals on numerous antidepressants.[98]

The control of psychiatric adverse effects is also a difficult challenge in TB management and such effects are related to worse prognosis and mortality.[107] Isoniazid, ciprofloxacin, ethambutol, and rifampicin, have been noted to be related to psychosis, with the evidence attributing this effect to isoniazid.[98] This adverse effect could be due to isoniazid's role as a MAOI, with influence on the catecholamines metabolism, potentially inducing a manic psychosis in individuals with mood alterations.[108] Delusions were described as the most common psychiatric symptom when isoniazid was administered, presenting around 4 weeks after the administration of the drug and among patients of around 35 years old.[7]

Another medication for TB from the second tier of drugs is cycloserine, which is a cell wall inhibitor and has the capacity to penetrate the blood–brain barrier.[98] It might help with the treatment of schizophrenia's negative symptoms. However, big doses like 250 mg/day and 1 g/day are related to anxiety, irritability, and depression.[105] This drug has shown 20%–33% rates for psychiatric side-effects including mania, insomnia and anxiety. It could also have more worrisome symptoms such as hallucinations, depression, euphoria, behavioral disorders, and suicidal ideation or attempts, usually appearing within the first 3 months of treatment.[7]

Fluoroquinolones are rarely associated with psychiatric side effects. The observation of psychiatric adverse reactions during treatment with ofloxacin or ciprofloxacin, like delirious states, paranoid, depressive and manic syndromes, sleep disturbances, and stupor, has also been documented.[7]

As shown, the understanding of the multiple interplay among the therapeutic alternatives is of utmost importance when dealing with TB-depression. Clinicians should be aware of the significant comorbidity between TB and mental illness, and the proper monitoring for the detection of psychiatric side-effects.[98]

Conclusion

TB remains a leading infectious cause of mortality worldwide, and the prevalence of DM and depression within the TB population will continue to grow in the upcoming years. Several questions remain unanswered regarding this complex and concurrent diseases. Multiple factors, ranging from biochemical aspects up to behavioral components are involved in the comprehension of the interplay between these comorbid diseases and TB that need to be translated, in the best scenario, to clear clinical guidelines. Better and integrated health services are required to meet the care necessities of these populations, along with an improvement in TB prevention, early diagnosis and comorbidities management. TB and its comorbidities conform a convoluted relationship, requiring a patient-centered care, compromising the social, economic and public health fields of the affected countries.

Author contribution(s)

Guillermo Cáceres: Conceptualization; Investigation; Writing – original draft; Writing – review and editing.

Rodrigo Calderon: Conceptualization; Investigation; Writing – original draft; Writing – review and editing.

Cesar Ugarte-Gil: Conceptualization; Investigation; Writing – original draft; Writing – review and editing.

ORCID iD

Cesar Ugarte-Gil https://orcid.org/0000-0002-2833-9087

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