Tuberculosis and Diabetes: another perfect storm?

By

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A dissertation submitted to Johns Hopkins University in conformity with the
requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
December 2016

1. <u>Abstract</u>

Objective

Tuberculosis is one of the most prevalent diseases worldwide, and is the most frequent infectious cause of death. Diabetes is also one of the most common non-communicable diseases worldwide, with substantial increases in low-and-middle income countries in recent years. Due to the synergy between these two diseases, low-and-middle income countries are facing difficulties to control both diseases, largely because there is no adequate information on tuberculosis-diabetes comorbidity. This study sought to improve the understanding of the co-occurrence of tuberculosis and diabetes in Peru, with the overarching aim to provide critical evidence to inform Peruvian disease control and health prevention programs.

Methods

First, we conducted a systematic review and meta-analysis in double high burden tuberculosis and diabetes countries was done to evaluate the role of Diabetes on Tuberculosis treatment outcomes. Second, to evaluate the epidemiology of diabetes in Peruvian tuberculosis patients, we conducted a cross-sectional study of 484 tuberculosis patients in Lima, evaluating diabetes prevalence and risk factors for the co-occurrence of tuberculosis and diabetes. Finally, mortality and factors associated with diabetes among tuberculosis multi-drug resistant (MDR-TB) patients in Lima was done using the information on the 1999 MDR-TB patients at the National Tuberculosis Program in Peru.

Results

In the systematic review, diabetes was associated with an increased risk for poor treatment outcomes among tuberculosis patients. Among Peruvian tuberculosis patients, diabetes was associated with older age and higher body mass index (BMI). In the cohort study among MDR-TB patients enrolled in Lima between 2010 and 2013, higher mortality was found among patients with diabetes, and MDR-TB patients with diabetes were associated with older age and higher BMI.

Conclusions

Tuberculosis-Diabetes comorbidity is more common in low-and-middle income countries like Peru than HIV. The presence of diabetes is associated with poor tuberculosis treatment outcomes and may put in jeopardy the advances in tuberculosis control in high burden countries. Considering the increasing incidence of diabetes in low-and-middle income countries, an adequate programmatic management involving both health programs (tuberculosis and diabetes) is required to reduce the burden of this comorbidity. Challenges at the health system level involving an adequate screening, including glucose test at Tuberculosis diagnosis and during the treatment may also be needed.

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3.   <u>Acknowledgements</u>

These almost 5 years of my PhD was, in several ways, an incredible period, professionally, but most important, at personal level. I had the opportunity to meet several outstanding professionals, who challenge and teach me with a lot of generosity. First, I would like to thank my advisor, Dr. Jonathan Golub, who has a lot of patience and make a lot of effort to support and guide me through a new setting for him (Lima, Peru), always with the honesty required at this training level, pushing me to make my best effort. Also, I want to thanks to Professor Robert Gilman, who push and help me to apply to this PhD, after that was my first advisor and the first friendly face at JHSPH. When I decide to change the topic and advisor, Bob was very supportive and he always demonstrated a special interest in my career, teaching me a lot about mentoring and science during our chats.

At JHSPH I have the opportunity to interact with a great group of amazing public health students, who gave to me a friendly support in a new city and in an exciting (but very intense) new academic adventure. Andrés, Ricardo, Javier, Gabriele, Manuela, Afsan, Mariana, Nick, Emma, Jonathan, Jessica, Claudia, Ian among others friends, gave me the sense of family in Charm City. During my activities at JHSPH, I had to interact with several faculty members who, with their example, teach me several issues for my professional and personal career. At US Cochrane Center, Prof. Kay Dickersin and Dr. Tianjing Li were extremely supportive and always interested in my career development, gave me the opportunity to participate actively in a great research group. Dr. Darcy

best I ever dreamed. Cynthia, as the clever and loving soul as she is, brought to our family Lucas, our puppy, who join me during these mornings, afternoon and nights of writing, reading and meditation in this dissertation work, making this time unforgettable and with several smiles during the process. Now, after this PhD work is over, Cynthia and I are starting the most important adventure of our life: parenthood, reason why I dedicate this work with all my love to my boy, Nicolas, who will join our family next year.

4.   <u>Support</u>

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7.   List of Abbreviations and Acronyms

AFB	Acid-Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
BMI	Body Mass Index
BTO	Bad Treatment Outcomes
CI	Confidence Interval
DM	Diabetes Mellitus
DM-1	Diabetes Mellitus type 1
DM-2	Diabetes Mellitus type 2
DMhbc	Diabetes high burden country
DOT	Directly Observed Treatment
FBG	Fasting Blood Glucose
HbA1c	Hemoglobin A1C or glycosylated hemoglobin
HIV	Human immunodeficiency virus
HO-1	Heme Oxygenase-1
HR	Hazard Ratio
IDF	International Diabetes Federation
IQR	Interquartile Range
IRB	Institutional Review Board
LMICs	Low and middle income countries
MAR	Missing at random
MDR-TB	Multidrug-resistant Tuberculosis
MeSH	Medical Subject Headings
MVN	Multivariate normal distribution
NCDs	Non-communicable diseases
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
PAF	Population attributable fraction
PCA	Principal Component Analysis
PHC	Primary Health Care
PR	Prevalence Ratio
REF	Reference
RR	Risk Ratio
SES	Socio Economic Status
SRDR	Systematic Review Data Repository
TB	Tuberculosis
TBhbc	Tuberculosis high burden country

TIMPs	Tissue Inhibitors of Metalloproteinase
UNION	International Union Against Tuberculosis and Lung Diseases
WHO	World Health Organization
WHR	Waist-to-Hip Ratio
XDR-TB	Extremely-resistant Tuberculosis

1. **Chapter One: Introduction and Review of the Literature**

1.1 Tuberculosis and Diabetes

Tuberculosis (TB) is one of the most ancient diseases in the history of humankind and one of the most prevalent among the communicable diseases until the present day (1). TB, which is caused by the bacteria *Mycobacterium tuberculosis*, was the first disease to be involved in a randomized clinical trial(2), and is one of the infections most studied in the last years (especially after the emergence of AIDS in the 1980s), but diagnostic tools remain poor and therapeutic options available are still imperfect (most of the drugs used in TB treatment are toxic, with several adverse events and long treatment times). Furthermore, drug-resistant *Mycobacterium tuberculosis* strains, such as multidrug-resistant (MDR-TB)(3) and extensively drug-resistant (XDR-TB)(4) are increasingly common, increasing the burden worldwide, especially in low- and middle-income countries(5). The usual location for TB is the lung, but it can affect many areas in the body, including bones, eyes, bladder and other organs(6).

Diabetes Mellitus (DM) is chronic disease and is classified in two types: type 1 (DM-1), which is defined as deficiency in insulin production, and type 2 (DM-2), defined as an insulin resistance, is a major public health problem in the present day and, like TB, is more prevalent in urban areas(7). As a one of the most prevalent non-communicable diseases, DM-2 is rising in low and middle-income countries in recent years(1, 8). DM-2 is a disease of insidious onset, with an often-late diagnosis, most frequently affecting middle and old-aged people; however it is increasing in young population in recent years(9-11). DM-2 is characterized by high levels of blood glucose, producing

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macrovascular and microvascular damage, and the clinical manifestations can be neuropathy, nephropathy, atherosclerosis and others(12). Unfortunately, there is not a cure yet, and the therapy is for life, dealing with adherence problems and complex approaches (diet, lifestyle behavior and complex drug therapy). Comorbidities is one of these problems in DM-2 patients, because is very common for patients to have more than one comorbidity, which can makes it difficult for the patient to maintain adequate blood glucose levels (13).

The association between TB and DM-2 has been known for many years: Bouchardat, one of the first doctors who studied DM (14), reported "tubercles" in DM patients lungs(15). At the beginning of 1900s, the frequency of DM among TB patients were around 50% (16). A manuscript published in 1957, reported a list of case series of TB-DM patients from 1930 to 1953, showing an mortality frequency among TB-DM patients between 11 to 100%(17). Nowadays, the association between TB and DM is supported by evidence that shows the association of bad TB treatment outcomes among TB-DM patients(18) and higher risk of TB infection among DM patients(19), increasing the double burden in these two diseases.

In this context, with the recent decades of increasing incidence of not only communicable but also non-communicable diseases (NCDs), the TB-DM epidemic is leading to a double burden in low and middle-income countries (where it is possible to find a DM-2 prevalence among TB patients close to 30%(20)), affecting not only the population health, but also, because affects middle-aged population who are usually the economic

support of their homes, the socio-economic development in these settings (21). After the re-emerging of TB in the last 30 years, specially with the increased incidence of MDR-TB and XDR-TB cases worldwide, this relation between TB and DM (specifically with DM-2) should be studied further, because there is a lack of evidence in different fields such as diagnostics, treatment (at patient level), but also in operational research and health systems research, to provide a better management to these affected communities(22).

1.2 *TB and DM interactions: Physiological, Clinical and Therapeutic issues*

1.1.1 *Physiological interaction between Tuberculosis and Diabetes Mellitus*

The association between TB and DM-2 began to receive attention in the 1900s (23, 24), but remains to be completely understood until today. One of the key concepts requiring research is the direction of this association; it is unclear whether TB infection makes patients more prone to development of DM-2 or whether DM-2 status increases susceptibility to TB infection(22, 25). While some studies support the hypothesis that TB leads to DM-2 (26, 27) because it creates a hyperglycemic state during infection and treatment, the majority of evidence seems to indicate that DM is a risk factor for TB(19).

DM-2 is a multi-organ disease affecting heart, lung, kidney, eyes, and brain, among other organs (28). The management of DM-2 is complex because it involves drug treatment, patient education, and close control of complications (such as cardiovascular or renal problems) (29). Obesity is one of the most important, if not the most important, risk factor for DM-2 (30, 31). However, not all overweight individuals develop DM-2: some

individuals are more susceptible because they are unable to adapt to higher caloric intake. The key components required to adapt to increased energy intake are in the pancreas(32). The islet β cells are responsible for maintaining normal levels of glucose, reducing the risk of insulin resistance and increasing subcutaneous adipose tissue rather than visceral adipose tissue (13). In diabetic patients, these cells are unable to compensate an α-cells increase glucagon secretion, causing uncontrolled hyperglycemia and insulin resistance, and leading finally to onset the of diabetes (33).

The immune response in individuals with DM-2 is not entirely understood too. Some studies have reported that an increase in adipose tissue also increases the production of pro-inflammatory cytokines (such as TNF- α, IL-6, IL-8, IL-12)(34-38). Studies in mice with DM-2 and TB showed increased pro-inflammatory cytokines (TNF- α, IFN-γ and IL-1b) with worse outcomes resulting in mice with TB and not DM-2 (39, 40). Adipocytokines (cytokines produced by the adipose tissue) is related in inflammatory process in obesity and DM(41), and the dysregulation of these adipocytokines can be related in the increased risk of TB among DM patients(42). Regarding a specific genetic expression in TB-DM patients, a pilot study found a reduction in the expression of two genes related to the macrophages (important in the immune response to *M. tuberculosis*): *HK2* and *CD28*(43). Furthermore, there is evidence about tissue damage (which is closely related with clinical severity) among TB-DM patients: Tissue Inhibitors of Metalloproteinase (TIMPs) and Heme Oxygenase-1 (HO-1) were associated with more tissue damage, and increased plasma levels of HO-1 and TIMP-4 were found among TB-DM patients compared with TB non-DM patients(44).

1.1.2   Clinical presentation of Tuberculosis and Diabetes

The clinical presentation among TB-DM patients compared with TB-non-DM patients has some differences: radiographic findings showed atypical presentations in TB-DM patients compared with TB non-DM patients (lower location vs apical location in the lung) (45) and lung cavities are more frequent in TB-DM(45-47). In a study evaluating MDR-TB patients with and without DM, a higher frequency of cavities were found among the DM patients(48). Glucose control has an important role too: patients who had an uncontrolled DM had higher odds to present lung cavities(46, 49).

There are also differences in the rate of smear and/or culture sputum conversion (usually used as a proxy of good TB treatment outcome and as a treatment follow-up biomarker): studies showed TB-DM patients takes longer to have a negative sputum test compared with non-DM(46, 47). Also, as in cavities, uncontrolled DM patients (patients with an HbA1c >7%) have higher odds to have 2nd month culture positive compared with non-DM patients(46).

1.1.3   Treatment of Tuberculosis and Diabetes

There are also challenges in TB treatment among DM patients, affecting treatment outcomes directly. An example is TB treatment: weight (specifically overweight and obesity is a problem in TB-DM patients) can affect rifampicin pharmacokinetics (50), but still there is not enough evidence if there is a different pharmacokinetics patter in TB-DM compared with TB-non-DM(51, 52).

There is not enough evidence of which DM treatment (insulin or metformin) is better for TB patients. In one hand, the first choice usually is insulin (an injectable hypoglycemic drug), which controls faster than other DM drugs the glucose level, however, the risk of hypoglycemia in patients with poor access to daily glucose measurement (such as TB patients, who usually don't have access to health insurance and/or money to cover a glucometer) is high. In the case of metformin (an oral hypoglycemic drug), is safer and doesn't require the same glucose control of insulin, but it has gastrointestinal adverse events (nausea, vomits) that can challenge the adherence to TB treatment(22). However, regarding metformin, there is preliminary evidence of beneficial effect of metformin, on the growth of *M. tuberculosis*, making metformin, regardless its role as DM drug, a potential candidate for co-adjunct drug in TB therapy(53), but further research is required.

1.3 *Epidemiological global status of Tuberculosis and Diabetes Mellitus*

1.3.1 *Worldwide situation of Tuberculosis*

TB, along with HIV infection, continues to be one of the most prevalent infectious diseases in the world, with 10.4 million new cases in 2015 and 1.4 million deaths, ranking with HIV as the leading cause for death from an infectious disease (54). TB is commonly termed a "poverty disease"(55) and it has significant societal impact, particularly among economically active segments of the population (56). The estimated population infected with *M. tuberculosis* is one-third of the world's population, and among those infected, 5% to 10% develop active TB(57). The key components for

worldwide control of TB are early detection of TB patients and cure rates high enough to interrupt transmission(6).

Progress has been made on several goals within the Global Plan to Stop TB 2011-2015(58), such as the decline of global incidence of TB in the last 2 years(59). However the rise of such complications as MDR-TB and XDR-TB, and comorbidities such as HIV and DM-2 are putting at risk the final goal of worldwide TB elimination by 2050(58).

1.3.2 *Worldwide situation of Diabetes*

In 2015, there were an estimated 415 million people living with DM worldwide, causing almost 5 million deaths in 2015(8). The estimated number of people with DM is projected to increase to 642 million by the year 2040, with a majority of DM affected populations living in low-resource settings (the estimate for 2015 was 75%)(8). A significant challenge is represented by the undiagnosed status of up to 179 million people with DM, leading with a late detection and the consequent presence of DM complications. The cost of DM is estimated to be 11% of total health spending in adult populations (8, 12).

One of the problems associated with DM (specifically DM-2) in low-middle income countries (LMICs) is the increased incidence of cases, affecting mostly middle-age and older population, struggling with their economy and development(7, 60). Also, in many of these countries, health systems are not prepared to manage DM-2, because around 90% of the expenditure on DM-2 is in high-income countries, so LMICs DM-2

population is vulnerable to related complications such as dialysis, limb amputation, blindness and others(7). However, high-income countries also have difficulties successfully engaging patients in care: one study in US showed around only 20% of DM-2 patients reached control goals (HbA1c, Blood Pressure, low-density lipoprotein cholesterol plus no smoking)(61).

1.3.3   *Worldwide situation of Tuberculosis-Diabetes Mellitus*

TB-DM comorbidity has been described increasingly during recent years, especially in low-and-middle income countries. Evidence shows a worst clinical presentation among TB-DM compared with TB non-DM, however there is no evidence on what is the best DM treatment in a situation of TB-DM, or how affects the immune response to TB treatment outcomes among TB-DM patients. However, predictions about how DM affects TB control were done, for example one projection based on a mathematical model showed how the increase of DM prevalence might jeopardize the reduction in TB incidence observed during recent years (62): with a 10% overall DM prevalence (based on the International Diabetes Federation –IDF- estimates in 2013), the incidence of TB will increase by 3% in 2035 compared with the estimated incidence without an increase in DM prevalence; furthermore, if the scenario considers that DM is a multi-factorial disease and factors such as obesity are increasing and DM prevalence is estimated to be 12.5%, the model estimates a change in TB incidence of 8% in 2035, showing how increasing prevalence of DM may directly affect the incidence of TB in coming years.

Unfortunately there is no information in the last Global Tuberculosis Report (2016) or in other World Health Organization o global report documents about TB-DM numbers worldwide (in contrast to TB-HIV figures for example), making it difficult to understand the real situation of this comorbidity(59). In 2011, the World Health Organization (WHO) in collaboration with the International Union Against Tuberculosis and Lung Disease, prepared the first framework for the management of TB-DM based on the evidence available at the moment, exposing the weakness of this evidence, and asking for more research in the area(63). Based on the epidemiology of TB and DM separately, it is possible to observe that among the 10 countries with highest burden of each disease, 7 countries (Brazil, India, China, Indonesia, Bangladesh, Pakistan and Russia) appear in both lists(7, 59)(Figure 1.1).

1.4 *Epidemiological situation in the Americas of Tuberculosis and Diabetes Mellitus*

1.4.1   Tuberculosis situation in the Americas

TB in the Americas region has already reached the goal for 2015 of 50% incidence reduction (since 1990 there has been a decrease in TB incidence from 56 per 100,000 habitants to 29 per 100,000 habitants), however TB is still a problem in countries such as Brazil, Bolivia, Haiti and Peru(59). In 2016, WHO reported that of 480,000 cases, were 2.9% were MDR-TB among new cases in the Americas (59). Comparing 1990 data with 2013 data, it is possible to observe that the percentage of patients younger than 15 years old increased slightly from 3.3% to 5.4%, but the ratio male/female remained stable during the same period (1.6 to 1.7)(59).

1.4.1   *Diabetes Mellitus situation in the Americas*

Latin America is undergoing an epidemiologic transition, with notable increases in the prevalence of hypertension, DM and hypertriglyceridemia, reaching levels comparable to the US and other developed countries (64). In the case of DM specifically, the estimated prevalence in the Americas in 2013 was 8% in the adult population, however this number is expected to increase in 60% by 2035(8). Among the countries with the highest number of people with DM are Brazil, Colombia and Argentina(8), and the countries with highest prevalence are Puerto Rico, Nicaragua and Dominican Republic (with prevalence higher than 11%). Regarding mortality, DM was the cause of 11.6% of all deaths in the region(8), increasing the burden among these countries.

A study in Argentina, Chile, Colombia and Mexico showed that in the period 2000-2011, 80% of the years of life lost due to DM were in people 50-74 years old (Mexico showed the biggest average lost)(65). Another study in Argentina, Chile y Uruguay showed a high prevalence of obesity, dyslipidemia and other risk factors (including DM-2 and Metabolic Syndrome prevalence of 12.4% and 37.4% respectively). These numbers reflect how the DM problem is increasing rapidly among Latin America countries, affecting the health costs (around US$65 billion in Latin America in 2000(66)).

1.4.1   *Situation in the Americas of Tuberculosis-Diabetes Mellitus*

Mexico and other countries are starting to have problems with TB-DM, in part due to the increase of DM incidence. Mexico, for example, reported around 20% of TB patients in the period 2000-2012 had also DM-2 (67). Most of them were female and with older age.

Other studies showed a greater severity in TB-DM cases, such as more lesions on chest X-ray and longer time with positive culture (47, 68, 69), which leads to worse treatment outcomes.

In Brazil, the number of TB-DM cases is increasing(70). One study in 2009 found that TB-DM patients in Brazil were older and more likely to die from TB than TB patients without DM (71). Another study in Chile showed a DM prevalence of 15.6% among TB patients (72). Similarly, to TB-DM worldwide data, there is not reliable data for TB-DM in Latin America because it is not routinely captured.

1.5 *Situation in Peru of Tuberculosis and Diabetes Mellitus*

1.5.1 *Tuberculosis situation in Peru*

Among the Latin American countries, Peru reports a high incidence of pulmonary TB (121 per 100,000 habitants)(54) and a growing incidence of MDR-TB, with a 4.5% increase from 1996 to 2004 (73). An estimated 58% of TB cases are concentrated in the capital city of Lima (74) and the majority of Peruvian TB patients are urban population. Despite the low prevalence of HIV when compared with the concentrated epidemic in some sub-Saharan African countries (75), the rise of MDR-TB incidence, years of poverty, and political conflict have fostered increasing TB incidence along with the ongoing problem of decreasing treatment success (from 83% in 1995 to 68% in 2010) (59).

There have been some changes in the demographics in recent years: the 2016 WHO TB Report showed an increase of young people (<15 years-old) and increase in the male/female ratio from 1.3 to 1.6 in the period 1990-2013 (59). Additionally 40% of MDR-TB cases are new cases with an increasing number of XDR-TB cases(59).

Since the 1990s, Directly Observed Treatment (DOT) has been the therapeutic approach for the treatment and control of TB in Peru (76). DOT consists of an intensive 2-month phase during which Isoniazid (H), Rifampicin (R), Ethambutol (E) and Pyrazinamide (Z) are administered in daily doses, followed by 4 months of bi-weekly doses of Isoniazid and Rifampicin (three times per week since 2014). The therapy is available in all health centers under the purview of the Ministry of Health. Patients attend these facilities for free TB diagnosis and treatment, including management of comorbidities such as HIV, depression and DM. Diagnostic tests for disease control include sputum smear for all cases of suspected TB and culture for all TB cases. In recent years, the growing MDR-TB epidemic has necessitated scale-up of universal testing for drug-resistant TB (77). It is evident in this context (including other factors such as social inequality(78, 79) or comorbidities such as depression(80)) that TB is, regardless of all the efforts since the 1990s, still far from being controlled in Peru.

1.5.1   Diabetes Mellitus situation in Peru

There is an increased number of studies in the last 5 years evaluating DM-II prevalence in Peru, with estimates around 9% in persons over 35 years old (81, 82) and pre-diabetes (defined as a fasting plasma glucose between 100-125 mg/dl) prevalence of 17.1%(81).

However, there is not a national register of DM patients, so potentially this prevalence is underestimate. Also, obesity, a key risk factor for DM-II has a prevalence in urban areas around 25% (31).

Unlike the Peruvian TB program, which has provided universal treatment and clinical care free of charge since the 1990s, the Peruvian program for NCDs has just started the implementation of a national program to provide free treatment for DM patients among poorer populations through National Health Insurance at the end of 2015. The increasing prevalence of diseases such as DM, requiring costly long-term care, constitutes a major challenge for the Peruvian health system.

1.5.1 *Situation in Peru of Tuberculosis-Diabetes Mellitus*

It is within this context that these two diseases – TB and DM – collide in Peru. Unfortunately, there is limited evidence on the real impact of diabetes on Peruvian TB patients, with only 4 observational studies were found in the literature. One was a cases series conducted among hospitalized patients(83), a second one was on patients with high risk of TB drug resistance and describing among them DM characteristics(84). The last two were publish in the last year years, one was comparing mortality between MDR-TB patients and non-MDR-TB patients, were DM was an independent risk factor for mortality(85) and the last one was a cohort study in a selected population in Lima, showing a there is difference in time to get a negative smear sputum test among TB-DM patients compared with TB-non-DM patients(86). All these studies describing DM among selected population, so is difficult to extrapolate the results to the general

Peruvian TB population. Two other studies explored pharmacokinetics of Rifampicin and Isoniazid in TB, TB-DM-II and TB-HIV patients, showing not difference in the median maximum plasma concentration (*Cmax*) among these populations(51, 52).

There have been efforts to improve local data and evidence on TB-DM: since the last National TB Peruvian Guidelines in 2013, there is universal screening for DM-II among all new TB cases (however the screening rate is around 60% at national level) (Personal Communication), but updated information about the national prevalence of DM among TB patients is not still available.

1.6 *Programmatic issues in the management of Tuberculosis and Diabetes Mellitus*

One significant problem is the integration of TB programs with DM care at Primary Health Care (PHC) level. One suggestion from WHO is the bi-directional screening for TB and DM-II among these groups of patients(63), but the evidence is still weak regarding screening of active TB among DM patients(22).

However, there are some experiences at PHC level (and some of them are based in previous experiences on TB-HIV integration)(87, 88) with varying degrees of success, but gaps remain (for example, describing the optimum transition for TB-DM patients in a DOT clinic, having successfully completed their TB treatment, to a DM clinic with an adequate care engagement) to be filled in this complex health problem. One study in Ethiopia showed most of the challenges are coming by the DM side: the continuity of DM care after TB treatment, unavailability of DM treatment and lack of training on DM

among health workers(89), requiring further local operational research and implementation science studies to fill these gaps. Glycemic control also is affected by poor capacity of health systems in LMICs to integrate health programs (Figure 1.2)(22).

1.7 *Rationale*

Both evidence and attention are increasing rapidly in the area of TB-DM. However, there are gaps in epidemiological information, necessitating further research especially in LMICs such as Peru. This dissertation will help to fill some of these gaps providing 3 studies: a systematic review, a prevalence study and a cohort study.

There have been several narrative reviews(25, 90, 91) and only two meta-analyses evaluating the TB-DM association(18, 19). One meta-analysis evaluated DM as a risk factor for TB (published in 2008)(19) and another examined the role of DM in TB treatment outcomes (published 2011)(18). Since these reviews (specifically the systematic reviews), there are reasons to evaluate new evidence on the topic:

- *There have been new studies since the most recent meta-analysis:* The last meta-analysis incorporated studies published until December 2010. Since then more than 50 new peer-reviewed articles have been published.

- *Study settings:* In both systematic reviews, a majority of the studies were conducted in developed country settings, such as the US and Japan. Given the concern over the impact of TB-DM in LMICs countries and the publication in

recent years of more studies in low-resources settings, it is important to evaluate potential differences in outcome based on setting.

Regarding the local status of TB-DM, DM is a growing problem in Peru, as in many developing countries. Unfortunately, there is no detailed data about the prevalence of DM-II and the clinical characteristics of Peruvian patients living with DM. Considering this, the proposed prospective prevalence study (with complete laboratory results, including HbA1c for all patients, and an initial exploration of potential risk factors in Peruvian TB-DM-II patients) provides the evidence required for actions at the National TB Program.

Finally, MDR-TB is one of the most significant problems in TB control in Peru (59), and there are some reports suggesting worse clinical and treatment outcomes among this population(48). As in the prevalence study, evidence is not available from Peruvian patients; this cohort study (which is the complete adult cohort of MDR-TB patients in Lima between 2010-2013) will therefore provide information on the characteristics of MDR-TB-DM-2 patients compared with MDR-TB non-DM patients, and also MDR-TB treatment outcomes among this population.

1.8 *Overall Goal and Specific Aims*

1.8.1   *Overall Goal of the Study*

A re-emerging TB epidemic combined with the continuous rise in DM prevalence in Peru is similar to other developing countries, creating a potential "perfect storm" with the collision of TB and DM. Thus, the overall goal of this dissertation is to strengthen the evidence base on the TB-DM association in Peru and globally with a 3 studies: a systematic review of TB treatment outcomes among TB-DM patients vs. TB non-DM patients in countries with high burden of TB and high burden of DM; a DM prevalence study among Peruvian TB patients, evaluating clinical characteristics; and a cohort study to evaluate differences in treatment outcomes among MDR-TB-DM patients vs. MDR-TB non DM patients in Peru.

1.8.2 Specific Aims

Specific Aim 1

To conduct a systematic review to determine whether TB-DM patients have worse TB treatment outcomes than TB-only patients in countries considered as high burden countries for TB and DM.

Specific Aim 2

To determine the prevalence of DM in recently-diagnosed Peruvian TB patients and identify the clinical and social characteristics and potential risk factors for DM among Peruvian TB patients.

Specific Aim 3

To determine the differences in treatment outcomes and patient characteristics in Peruvian MDR-TB-DM patients compared with MDR-TB non-DM patients

1.9 Figures

Figure 1.1 .– Countries with Tuberculosis and Diabetes double burden

22 countries with High TB burden (WHO)

China India Brazil Bangladesh Indonesia Pakistan Russia

Top ten countries for number of adults with diabetes(IDF)
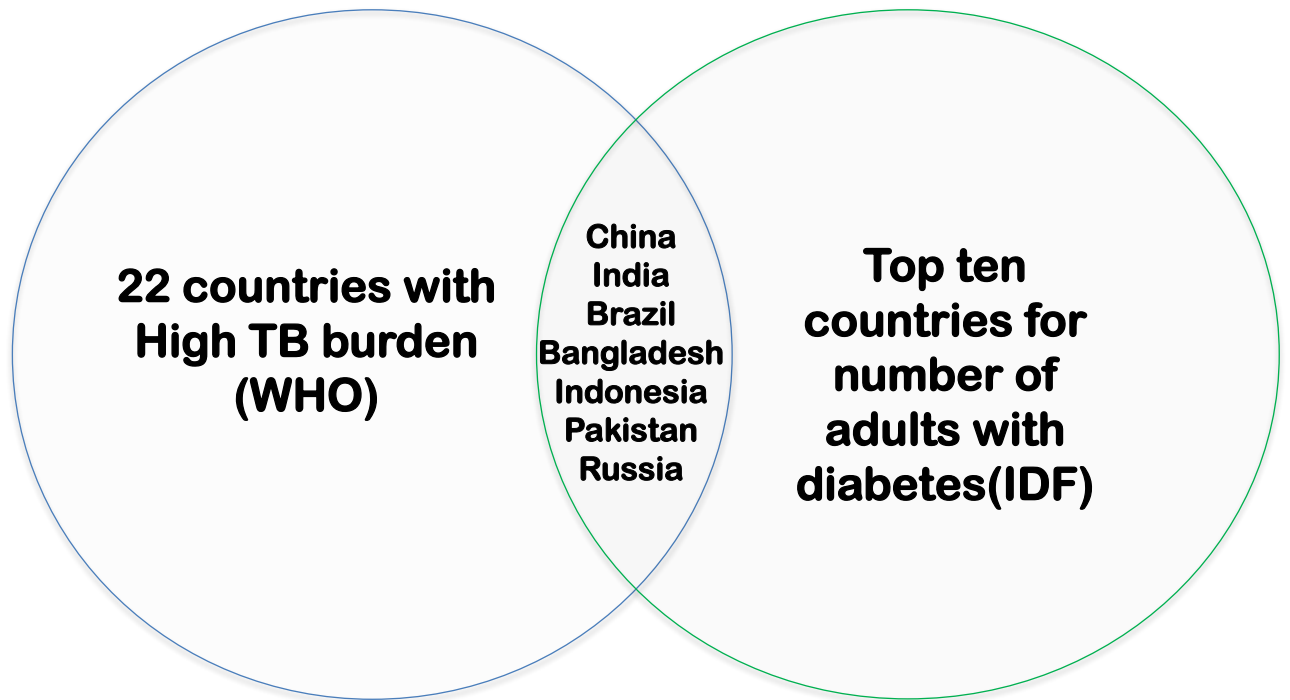
IDF Diabetes Atlas Seventh Edition 2015; Global Tuberculosis Report. WHO 2015

Definition of countries with TB-DM double burden dual high burden if they are listed by WHO as TB high burden country and as high DM prevalence country by the International Diabetes Federation

Figure 1.2 .- Factors that affect glycemic control in TB patients

Drug therapy
Side-effects (eg, vomiting);
drug–drug interactions;
weight gain during treatment

Active tuberculosis
Inflammation leading to:
weight loss; loss of appetite;
insulin resistance

Behaviour
Variable food intake;
physical activity;
treatment compliance

Health systems
Access and affordability of health services;
collaboration between tuberculosis and
diabetes physicians; laboratory facilities;
continuous medicaton supply

Figure from Riza AL, Pearson F, Ugarte-Gil C, et al. Lancet Diabetes 2014 (22)

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2.   Chapter Two: Paper I

Risk of death and/or poor treatment outcomes among persons with tuberculosis and diabetes in high-burden tuberculosis & diabetes countries: a systematic review and meta-analysis

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Abstract

Background

The impact of diabetes mellitus (DM) in persons with tuberculosis (TB) has recently received increased attention globally. A systematic review (studies published through Dec 2010) examined the association between DM and TB treatment outcomes, but the majority of included studies were conducted in high-income countries. Given the concern over the impact of diabetes in countries with a high burden of both TB and DM (TBhbc & DMhbc), many new studies have been published recently. We systematically reviewed the literature through 2015 to determine if the association differs by TBhbc & DMhbc settings.

Methods

The search was conducted in 6 bibliographic databases and all languages. We included cohort and case-control studies investigating treatment outcomes between TB patients with DM (TB-DM) and TB patients without DM (TB non-DM). Two reviewers independently screened abstracts, full-texts, and extracted data. The methodological quality and risk of bias of the included studies were assessed according to Newcastle-Ottawa Scale. Random-effect meta-analysis was used for data synthesis and main analyses.

Results

The literature search yielded 16,770 articles; 355 full-texts were reviewed; of these we included 11 from TBhbc & DMhbc. TB-DM patients had an increased risk of death compared with TB patients in the pooled analysis (Pooled Relative Risk pRR=2.5, 95%CI: 1.8-3.3; I^2:51%); TB-DM patients had higher risk of poor outcome (treatment failure or death) compared with TB non-DM patients (pRR=2.6, 95%CI: 1.6-4.3; I^2=69%). Among the studies with confirmed DM status, the pRR for Death was 2.5 (95%CI 1.2-5.1; I^2=48%) and the pRR for poor outcome was 2.5 (95%CI 1.5-4.2; I^2=70%). An asymmetrical funnel plot suggests potential publication bias.

Conclusions

TB-DM patients had higher risk of unsuccessful TB treatment outcomes compared with TB non-DM patients from TBhbc & DMhbc. Prospective and well-designed studies are needed to evaluate factors associated with poor treatment outcomes among TB patients.

Keywords: **Tuberculosis, Diabetes Mellitus, treatment outcomes**

Introduction

The impact of diabetes mellitus (DM) on tuberculosis (TB) risk and treatment outcomes has received increased attention in recent years, considering the rising incidence of non-communicable diseases (NCDs) in the past few decades(1) and a slowly declining global TB incidence (2). The TB-DM epidemic is leading to a double burden in low and middle-income countries (LMICs), reaching levels of DM prevalence more than 20% among TB patients in some settings (3-10).

Despite the achievements in the last years reducing TB incidence, the success of WHO's End TB strategy (elimination of TB by 2035) can be affected by several factors including weak health systems, social determinants, DM and others(11). Regarding DM, a projection based on a mathematical model showed how the increase of DM prevalence might jeopardize the reduction in TB incidence observed during recent years (12): with a 10% overall DM prevalence, the incidence of TB will increase by 3% in 2035 compared with the estimated incidence without an increase in DM prevalence. Furthermore, if the scenario considers that DM is a multi-factorial disease and factors such as obesity are increasing and DM prevalence is estimated to be 12.5%, the model estimates a change in TB incidence, increasing by 8% in 2035. These results suggest how increasing prevalence of DM may directly affect the incidence of TB in coming years(12).

There is evidence that DM worsens TB clinical presentation and leads to poorer treatment outcomes and greater risk of death (13-17). Also, TB patients with DM have been shown to have more lung damage and higher frequency of cavities(16), slower culture(13) and smear (16-18) conversion and higher risk of multidrug resistance (19). A systematic review published in 2011 summarized evidence on TB treatment outcomes among TB patients with DM (including 33 primary studies published until 2010), though only 5 studies were conducted in high burden TB or DM countries. The review reported higher risk (RR: 1.7; 95% CI 1.4 -2.1) of poor TB treatment outcomes among TB-DM patients compared with TB non-DM(20). However, since publication, more than 60 papers have been published evaluating TB treatment outcomes among TB-DM patients, and many

from high burden TB and DM countries were published, providing new evidence for an update. The impact of TB-DM on patients in these countries should be evaluated, especially because most of the studies included in Baker *et al* review were not primarily designed to evaluate the association of TB-DM with TB treatment outcomes, and the methodological quality of these primary studies was not optimal, expecting a better and less biased studies in this new review.

We aimed to evaluate if TB-DM have worse TB treatment outcomes than TB non-DM patients, updating the study published by Baker *et al*(20), but focused in countries considered with double high burden on TB & DM, with the goal to evaluate the impact of TB-DM in these settings.

Methods

Search strategy and selection criteria

The primary objective of this systematic review and meta-analysis is to estimate the difference in TB treatment outcomes between TB-DM patients and TB non-DM patients in countries high burden of TB and DM and was registered at PROSPERO Register (#42015026927). We sought to identify peer reviewed, studies containing data on TB outcomes among patients with and without DM. We searched the following electronic scientific journal databases from the 1/1/1980 up to 30/04/2015; Medline (via PubMed), Embase (via Embase.com), AIM, LILACS, IMEMR, IMSEAR and WPRIM (via WHO global index medicus). The start date was chosen as by this point because the standard 6-month TB treatment was in common use as a mainstay TB treatment thus TB regimens across studies should be more comparable(21). We used both MeSH and keyword terms (tuberculosis, diabetes mellitus, risk factor, outcome) in combination with standard Boolean operators to create a highly sensitive search strategy (see appendix 1). We also identified potentially relevant titles through conference proceeding searches, contacting specialists in the field and completing a citation search (via Scopus) for the first review of TB-DM outcomes.

The search was not narrowed beyond these broad categories in order to standardize search strings across databases and to maximize the search. The literature identified from the databases noted above was combined into a single bibliographic database. Duplicates of the retrieved studies were removed. Once this was completed, titles and abstracts were screened: the primary search included articles of all types, without any restriction on publication year or language of publication. During secondary screening, review articles, editorials and letters, as well as those not meeting our inclusion criteria outlined above were excluded.

Eligibility Criteria

We included various study designs in the review: cohort studies (prospective or retrospective), case-control studies or any study with longitudinal follow-up of TB treatment outcomes. To define a country as a TB & DM double high burden country (TB & DM dhb), we considered if the country had comparative prevalence >10% in the adult population (over 20 years of age) (according to the IDF diabetes atlas)(22) and if is listed as high burden country for TB by WHO(2). Regarding population, we included studies with patients on standard TB treatment(23), and exclude studies only focused in MDR-TB treatment outcomes because they have different TB treatment length. DM status was defined as is defined in the primary study (medical records, fasting blood glucose, HbA1c). The primary outcome utilized in this review is TB treatment outcome. We use the definitions for TB treatment outcome by WHO(24).

Data Extraction and Quality Assessment

Two independent reviewers (from among CU-G, PH, FP) were involved in the review of titles/abstracts and the full text of articles, and a third reviewer (JC) within the team solved the discrepancies. If the title/abstract record did not provide enough information for inclusion, then the full text was retrieved for full text screening. For the data extraction, the study team developed ad-hoc forms for data extraction and study quality, using the Systematic Review Data Repository (SRDR) on-line platform(25), with double data entry to reduce the risk of error in the abstraction process. The information abstracted included demographic characteristics (age, sex), country, year, DM definition,

anthropometric measures (Body Mass Index), glucose test (fasting blood glucose, random blood glucose, HbA1c), type of TB (pulmonary or extra pulmonary), number of episodes of TB, sputum smear and culture results and TB treatment outcomes.

Regarding methodological quality of included studies, observational studies in general are prone to confounding and bias (in addition to the role of chance if the study is of low power to see the difference stated in the hypothesis) to some degree depending on the design. The source of bias of each full text study will be evaluated independently by each reviewer using Newcastle-Ottawa Scale (26), which is a tool for observational studies. Overall quality of the evidence found was described in a GRADE Summary of Findings table(27).

Statistical Analysis

The analysis was done use RevMan (version 5.3). We pooled measures of association on treatment outcomes, using inverse variance weighting in a random-effects model. We estimated heterogeneity with I^2 statistic (a value greater than 50% will be considered as important statistical heterogeneity) and Chi-square test for heterogeneity (p value <0.05 is consider as significant heterogeneity). Also, forest plots were evaluated to examine the degree of overlap between confidence intervals of risk estimates of the included studies. To assess the potential risk of publication bias, a funnel plot was drawn (28).

Role of the funding source

The sponsors of this study had no role in the study design, development or in the preparation of this manuscript.

Results

The literature search yielded 16,770 articles; 94 full-texts were reviewed; of these 13 were conducted in countries with a high burden of both TB & DM (Figure 2.1)(13, 14, 16-18, 29-35). The TB characteristics of the primary studies are in Table 2.1 and the DM characteristics are in Table 2.2. These studies included 38,644 TB patients and 3,497 TB-

DM patients in Brazil (4 studies), China (2 studies), India (4 studies), Indonesia (1 study) and Russia (2 study). Eight of 13 studies were retrospective cohorts, 2 were case-control studies(34, 35) and DM definition was made mainly by medical records.

11 studies remained eligible to pool to estimate an effect measure. Patients with both TB and DM had an increased risk of death compared with TB patients without DM in the pooled analysis (Pooled Relative Risk pRR=2.5, 95%CI: 1.8-3.3; I^2:51.1%) (Figure 2.1). TB-DM patients had higher risk of poor outcome (treatment failure or death) compared with TB-nonDM patients (pRR=2.6, 95%CI: 1.6-4.3; I^2: 69%) (Figure 2.3). Only one study (13) reported sputum culture conversion as treatment outcome, showing no association with TB-DM status (adjusted OR: 0.9, 95%CI: 0.3-2.7). Only 3 studies reported TB treatment outcome adjusted by potential confounders(13, 29, 36) and one reported relapse as treatment outcome (crude OR: 2.4, 95%CI:0.6-10.4)(34).

A sensitivity analysis was done evaluating studies with confirmed DM status, the risk to death was similar (pRR=2.5; 95%CI: 1.2-5.1; I^2: 48%) and the same occurs with the risk for TB treatment outcome (pRR=2.5; 95%CI: 1.5-4.2; I^2: 70%) (Figures 2.4 and 2.5). Regarding publication bias, the funnel plot was symmetrical (Figure 2.6), suggesting low risk of publication bias.

Regarding quality of the studies, the NOS Quality Score was in overall 6.8, when the lowest had 6 and the highest had 8 as NOS Score. The assessment of quality is explained in Table 2.3. Regarding the quality of the body of evidence among the studies included in the meta-analysis, the outcomes are summarized in Table 2.4 using the GRADE approach. The findings showed a low level of quality, mainly because all the studies included were observational with some problems in the design.

Discussion

Our results confirm the association found by Baker *et al*(20) on poor TB treatment outcomes among TB-DM patients, however our estimate were higher than theirs for risk

of death (pRR=2.5 vs pRR=1.9) and risk of poor TB treatment outcomes (pRR=2.6 vs pRR=1.7). The difference in magnitude of the point estimate can be explained because our review focused in LMICs countries with a high burden of both TB and DM. DM care, as any chronic disease in LMICs, has a large economic burden in these settings(37), and requires adequate health monitoring and a stronger health system to provide diagnosis, care and treatment. Studies in India(38) and Indonesia(39) showed how complex is DM care in these health systems, affecting DM care especially among poorest population, which also are in higher risk for TB.

Epidemiological characteristics are also different by settings: in high-income countries, men usually have higher frequency of DM compared with women, unlike LMICs, where women have more DM than men(40). TB is still frequent in LMICs(2, 41), but in high-income countries is more frequent among older population(42). Age is a strong associated factor for DM, and because older populations in LMICs have inadequate and incomplete access to health care(43, 44), this population is at high risk for TB-DM comorbidity.

Besides health systems factors related with TB-DM at LMICs, there are others: genetically DM is associated with higher risk in these populations (Latin America, South Asia and Africa populations)(45-47) in the same way as TB is associated with same populations(48-52). Also, despite the last improvements in TB burden reduction worldwide, the number of cases is still high among these populations(2), and the projected increase of DM among same populations in the following years(22), would complicate disease control for TB-DM(53).

Because many of the studies used in this review and in Baker *et al*(20) were not aimed to evaluate TB-DM association, there is a lack of confounding control in general: in our review only three studies (13, 29, 36) reported adjustment by confounders and in Baker's review only 4 studies(54-57)(3 studies in USA and one in Taiwan). Regardless NOS Quality Score didn't cover all sources of potential biases (and didn't consider the role of chance too), we observed that none of included studies in our review considered to adjust

for important confounders such as HbA1c, comorbidities (as hypertension, renal failure), BMI (only one study (13) adjusted by BMI), DM treatment, smoking, and gender, which are related with DM mortality(58, 59). Also, other reasons of death such as cancer (which are associated with DM)(60, 61), was not evaluated in these studies because TB specific mortality is not usually reported. The overall summary of findings (showed in Table 2.4) confirms the low quality of the evidence.

The strength of our review is the comprehensive search of TB-DM without restrictions of language in several bibliographic databases with broad search terms, because in many cases DM was not consider as an exposure, reason why we screened more than 16000 hits evaluating TB treatment outcomes in general with the aim to reach as many DM exposure measures as possible. Regarding the restriction of year (1980), most of the studies using WHO regimen for drug sensitive TB (rifampicin-based regimens) were publish after 1980(62, 63), reason why there is not too much heterogeneity regarding TB treatment (and TB treatment length).

There are some limitations, like any meta-analysis done among observational studies, mainly based on the quality of the included primary studies. One was the definition of DM in the included studies, because DM status was not routinely assessed in TB programs and/or epidemiological TB studies in general, underestimating the association between TB-DM and poor TB treatment outcome. However, when sensitivity analysis was done in only studies with confirmed DM status (13, 14, 16-18, 29-33), the estimate direction for death and poor treatment outcome were kept. Also, hyperglycemia is very common in infectious diseases(64, 65), including TB, affecting DM diagnosis in TB patients (especially if it was done at TB diagnosis), increasing the risk of DM misclassification, because it can be a transient hyperglycemia episode rather than DM(66, 67). However, hyperglycemia status (no DM) are associated with poor TB treatment outcomes compared with normoglycemic TB patients(67). Glucose control during TB treatment was not recorded in these studies, and this is an important factor to evaluate the severity of DM in general, furthermore, glucose control among TB-DM patients is also associated with TB treatment outcomes: a study done in Taiwan showed that poor

glucose control was associated with poor TB treatment outcomes among TB-DM patients (68).

Our review confirmed the association between TB-DM and poor TB treatment outcomes in TB-DM double high burden countries, similar that founded in high-income countries. The risk for mortality and treatment failure should be evaluated in detail in future studies, looking for DM complications that can affect the success of TB treatment (renal failure, cardiovascular complications) and taking account known confounders in the analysis (such as HbA1c, BMI, gender). Considering the ageing of TB population(42), and the strong association of TB-DM with age, there is a necessity to implement comprehensive TB-DM care in TB clinics, including close glucose monitoring and DM treatment as part of TB care among TB-DM patients, with an special emphasis in elderly population.

Figures

Figure 2.1 – Flowchart for study selection

Figure 2.2 – Risk of Death among TB-DM and TB non-DM

Study or Subgroup	TB-DM Events	Total	TB Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Alisjahbana 2007	2	94	0	540	1.0%	28.47 [1.38, 588.46]	
Hongguang 2015	9	182	9	944	8.0%	5.19 [2.09, 12.89]	
Mathew 2006	8	44	75	1872	11.9%	4.54 [2.33, 8.82]	
Mi 2013	2	97	2	483	2.3%	4.98 [0.71, 34.92]	
Nandakumar 2013	42	677	71	2127	19.4%	1.86 [1.28, 2.69]	
Orofino 2012	3	14	15	294	5.9%	4.20 [1.37, 12.84]	
Reis-Santos 2013	73	703	995	17047	23.6%	1.78 [1.42, 2.23]	
Ribeiro 2013	39	302	712	12472	21.5%	2.26 [1.67, 3.06]	
Sangral 2012	2	23	16	257	4.1%	1.40 [0.34, 5.70]	
Viswanthan 2013	0	96	5	149	1.1%	0.14 [0.01, 2.51]	
Viswanthan 2014	1	89	1	120	1.2%	1.35 [0.09, 21.27]	
Total (95% CI)		**2321**		**36305**	**100.0%**	**2.45 [1.80, 3.33]**	
Total events	181		1901				

Heterogeneity: Tau² = 0.09; Chi² = 20.56, df = 10 (P = 0.02); I² = 51%
Test for overall effect: Z = 5.70 (P < 0.00001)

Error bars show 95%CIs. Risk Ratios and weights were derived from Inverse Variance Random Effects model

Figure 2.3 – Risk of Death or treatment failure

Study or Subgroup	TB-DM Events	TB-DM Total	TB Events	TB Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Alisjahbana 2007	8	94	32	540	14.2%	1.44 [0.68, 3.02]	
Hongguang 2015	15	182	14	944	14.6%	5.56 [2.73, 11.31]	
Mi 2013	12	97	13	483	14.1%	4.60 [2.16, 9.77]	
Nandakumar 2013	74	677	148	2127	19.9%	1.57 [1.20, 2.05]	
Orofino 2012	4	14	21	294	12.1%	4.00 [1.59, 10.09]	
Sangral 2012	4	23	24	280	11.6%	2.03 [0.77, 5.35]	
Viswanthan 2013	4	96	6	149	9.0%	1.03 [0.30, 3.57]	
Viswanthan 2014	8	89	1	120	4.5%	10.79 [1.37, 84.69]	
Total (95% CI)		1272		4937	100.0%	2.63 [1.61, 4.29]	
Total events	129		259				

Heterogeneity: Tau² = 0.30; Chi² = 22.37, df = 7 (P = 0.002); I² = 69%
Test for overall effect: Z = 3.86 (P = 0.0001)

Error bars show 95%CIs. Risk Ratios and weights were derived from Inverse Variance Random Effects model

41

Figure 2.4 – Risk of Death among TB-DM and TB non-DM in studies with confirmed DM status

Study or Subgroup	TB–DM Events	Total	TB Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Alisjahbana 2007	2	94	0	540	5.0%	28.47 [1.38, 588.46]	2007	
Sangral 2012	2	23	16	257	15.7%	1.40 [0.34, 5.70]	2012	
Mi 2013	2	97	2	483	10.2%	4.98 [0.71, 34.92]	2013	
Nandakumar 2013	42	677	71	2127	34.0%	1.86 [1.28, 2.69]	2013	
Viswanthan 2013	0	96	5	149	5.5%	0.14 [0.01, 2.51]	2013	
Viswanthan 2014	1	89	1	120	5.9%	1.35 [0.09, 21.27]	2014	
Hongguang 2015	9	182	9	944	23.6%	5.19 [2.09, 12.89]	2015	
Total (95% CI)		**1258**		**4620**	**100.0%**	**2.45 [1.18, 5.09]**		
Total events	58		104					

Heterogeneity: Tau² = 0.37; Chi² = 11.60, df = 6 (P = 0.07); I² = 48%
Test for overall effect: Z = 2.40 (P = 0.02)

Error bars show 95%CIs. Risk Ratios and weights were derived from Inverse Variance Random Effects model

Figure 2.5 – Risk of Death or treatment failure in studies with confirmed DM status

Study or Subgroup	TB-DM Events	TB-DM Total	TB Events	TB Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Alisjahbana 2007	8	94	32	540	16.2%	1.44 [0.68, 3.02]	2007
Sangral 2012	4	23	24	280	13.2%	2.03 [0.77, 5.35]	2012
Viswanthan 2013	4	96	6	149	10.4%	1.03 [0.30, 3.57]	2013
Mi 2013	12	97	13	483	16.0%	4.60 [2.16, 9.77]	2013
Nandakumar 2013	74	677	148	2127	22.3%	1.57 [1.20, 2.05]	2013
Viswanthan 2014	8	89	1	120	5.2%	10.79 [1.37, 84.69]	2014
Hongguang 2015	15	182	14	944	16.6%	5.56 [2.73, 11.31]	2015
Total (95% CI)		**1258**		**4643**	**100.0%**	**2.48 [1.46, 4.23]**	
Total events	125		238				

Heterogeneity: Tau² = 0.31; Chi² = 20.17, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 3.36 (P = 0.0008)

Error bars show 95%CIs. Risk Ratios and weights were derived from Inverse Variance Random Effects model

Figure 2.6.- Funnel plot assessing Publication Bias
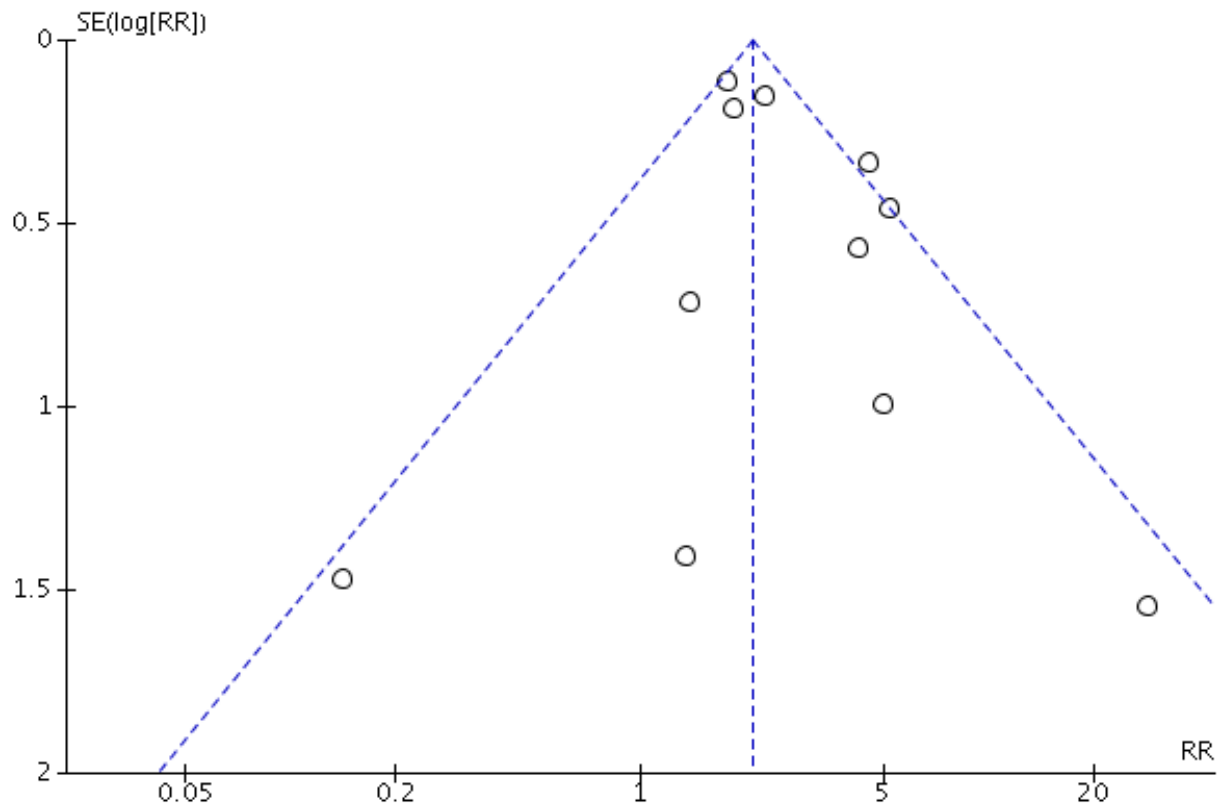
Tables

Table 2.1. – TB Characteristics of included studies for the association between DM and TB outcomes

Study	Type of Study	Country	Type of TB	Total	New TB case (%)	Population with TB-DM (%)	Outcomes				Variables adjusted for outcome
							Sputum culture conversion	Failure and Death	Death	Relapse	
De Oliveira, 2000	Case-control	Brazil	Pulmonary TB	361	NR	Case 6(11%) Control 5 (5%)				X	
Mathew, 2006	Retrospective cohort	Russia	Undifferentiated TB	1916	1656 (86.4%)	44 (2.3%)			X		Age, gender, TB retreatment, MDR, Alcoholism
Kourbatova, 2006	Case-control	Russia	Undifferentiated TB	460	NR	20			X		
Alisjahbana, 2007	Prospective cohort	Indonesia	Pulmonary TB	634	602 (95.0%)	94 (14.8%)	X	X	X		Age, gender, BMI, drug resistance, adherence
Orofino, 2012	Retrospective cohort	Brazil	Undifferentiated TB	311	83 (26.7%)	14 (4.5%)		X	X		
Sangral, 2012	Retrospective cohort	India	Undifferentiated TB	280	Not reported	23 (8.2%)		X	X		
Mi, 2013	Retrospective cohort	China	Undifferentiated TB	1589	1453 (91.4%)	189 (11.9%)		X	X		
Nandakumar, 2013	Retrospective cohort	India	Undifferentiated TB	2794	2708 (96.9%)	667 (23.9%)		X	X		
Reis-Santos, 2013	Retrospective cohort	Brazil	Undifferentiated TB	17047	24145 (77.7%)*	1797 (5.8%)			X		Age, Institutionalization, TB form, initial smear, Treatment type
Ribeiro, 2013	Retrospective cohort	Brazil	Undifferentiated TB	12795	Not reported	323 (2.5%)			X		
Viswanthan, 2013	Retrospective cohort	India	Undifferentiated TB	245	Not reported	96 (39.2%)		X	X		
Viswanthan, 2014	Prospective cohort	India	Undifferentiated TB	209	177 (84.7%)	89 (74.2%)		X	X		
Hongguang, 2015	Prospective cohort	China	Pulmonary TB	1126	88 (7.8%)	182 (16.1%)		X	X		

*Not reported among patients with TB treatment outcome info

Table 2.2. – DM Characteristics of included studies for the association between DM and TB outcomes

Study	Mean Age (SD)	Mean Age TB-DM (SD)	Mean BMI (SD)	Mean BMI TB-DM (SD)	DM treatment (%)	New DM Case (%)	DM Case Definition
De Oliveira, 2000	42.6 (NR)*	NR	NR	NR	NR	NR	Medical Records
Mathew, 2006	43.6 (NR)	NR	NR	NR	NR	NR	Medical Records
Kourbatova, 2006	43 (NR)	NR	NR	NR	NR	NR	Medical Records/ Self-report
Alisjahbana, 2007	NR	45.0 (39.8-52.0)[a]	NR	21.1 (18.9-22.8)[a]	NR	57 (61.3%)	FBG > 126 mg/dL 2 times
Orofino, 2012	39 (NR)	NR	NR	NR	NR	NR	Medical Records
Sangral, 2012	41.0 (NR)	50.1 (14.4)	NR	NR	NR	NR	Medical Records, GOD-POD or OTTG
Mi, 2013	NR	NR	NR	NR	NR	NR	FBG > 126 mg/dL 2 times
Nandakumar, 2013	NR	NR	NR	NR	NR	NR	Medical Records, FBG > 126mg, RBG > 200mg or PPBS
Reis-Santos, 2013	NR	52 (14)	NR	NR	NR	NR	Medical Records
Ribeiro, 2013	NR	NR	NR	NR	NR	NR	Medical Records
Viswanthan, 2013	42.4[b]	49.9 (11.3)	17.9	18.9 (4.1)	NR	NR	Medical Records, FBG > 126 mg/dL, OTTG
Viswanthan, 2014	NR	50	NR	NR	NR	NR	Medical Records, OTTG
Hongguang, 2015	NR	53 (45-64)[a]	NR	NR	NR	NR	Medical Records, FBG > 126 mg/dL, OTTG

NR: Not Reported

FBG: Fasting Blood Glucose; GOD-POD: Glucose Oxidase-Peroxidase Method; OTTG: Oral Glucose Tolerance Test; PPBS: Postprandial blood sugar

[a]: Median (IQR) ; [b] : Median

* Calculated from age-group information

Table 2.3. –Assessment of Quality by the use of the Newcastle-Ottawa Scale (NOS)*

Study ID	Selection				Comparability	Outcome			NOS Quality Score (number of stars)
	Representativeness of the Exposed cohort	Selection of the Non Exposed Cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at baseline	Comparability of Cohorts on the Basis of the Design Analysis	Assessment of Outcome	Adequate length of Follow-up	Adequacy of Follow-up of cohorts	
Mathew, 2006	★	★	★	★		★	★		6
Alisjahbana, 2007	★	★	★	★	★	★	★	★	8
Orofino, 2012	★	★	★	★		★	★		6
Sangral, 2012	★	★	★	★			★	★	6
Mi, 2013	★	★	★	★		★	★	★	7
Nandakumar, 2013	★	★	★	★		★	★	★	7
Reis-Santos, 2013	★	★	★	★	★	★	★	★	8
Ribeiro, 2013		★	★	★		★	★	★	6
Viswanthan, 2013	★	★	★	★		★	★	★	7
Viswanthan, 2014	★	★	★	★			★	★	7
Hongguang, 2015	★	★	★	★		★	★	★	7

*For cohort studies

Table 2.4. –Assessment of overall evidence quality using GRADE methodology*

# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TB-DM	TB	Relative (95% CI)	Quality	Importance
			Quality assessment				Number of patients		Effect		
Death (assessed with: study defined measures)											
11	observational studies	not serious	not serious	not serious	not serious	none	181/2321(7.9%)	1901/36305 (5.2%)	**RR 2.45** (1.80 to 3.33)	⊕⊕◯◯ LOW	CRITICAL
Bad Treatment outcome (Death and Failure assessed with: study defined measures)											
8	observational studies	not serious	serious	not serious	not serious	none	129/1272 (10.1%)	259/4937 (5.2%)	**RR 2.63** (1.61 to 4.29)	⊕◯◯◯ VERY LOW	CRITICAL

*For studies included in the meta-analysis

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3. <u>Chapter Three: Paper II</u>

Prevalence and Factors associated with Tuberculosis and Diabetes Mellitus co-morbidity among Peruvian Population

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Abstract

Introduction

Diabetes mellitus (DM) prevalence is increasing around the world, especially in low and middle income countries (LMICs). Tuberculosis (TB) is still a public health problem in LMICs, such as Peru, where there is limited evidence about DM prevalence and its associated factors among TB patients. We evaluated the prevalence and associated factors of DM among TB patients in Lima, Peru.

Materials and Methods

We conducted a cross-sectional study based in the Peruvian research site of the TANDEM Consortium (www.tandem-fp7.eu). Adults from 4 health centers in Lima with a recent diagnosis of TB were screened for DM using HbA1c. Clinical, anthropometric and socio-demographic characteristics were collected. Poisson regression modeling with robust variance was used to calculate prevalence ratios for associated factors.

Results

484 TB participants were enrolled, and 44 were determined to have DM (Prevalence 9.1%; 95%CI: 6.8%-12.0%); 28 had pre-existing DM and 16 were newly diagnosed at screening. DM prevalence among those over 35 years of age was 18.1% (95%CI: 13.5%-23.8%) and 1.9% (95%CI 0.8%-4.4%) among those under 35. Pre-diabetes prevalence (defined as HbA1c between 5.7%-6.4%) was 25.6% (95%CI: 21.9%-29.7%) among all participants and 27.3% (95%CI: 21.8%-33.7%) among individuals over 35 years of age. In Poisson regression, age over 35 years old and a BMI higher than 30kg/m^2 were associated with DM in adjusted analyses. When restricted to participants over 35 years of age, these risk factors did not change.

Conclusions

DM was more common in TB patients over 35 years old and in obese individuals. Further studies are needed to evaluate pathophysiology, epidemiology, and transmission patterns within TB-DM populations.

Keywords: Tuberculosis, Diabetes, Prevalence

Introduction

Among the Latin American countries, Peru reports one of the highest incidences of pulmonary tuberculosis (TB) (119 per 100,000 habitants in 2015)(1). 5.3% of Peruvian TB patients have multi-drug resistant tuberculosis (MDR-TB), and treatment success is reported to be 79%. Primarily an urban disease, an estimated 58% of TB cases are concentrated in the capital city of Lima (2).

Diabetes mellitus (DM) is a growing problem in Peru, as in many low and middle income countries (LMIC)(3). Recently, some studies conducted in Peru reported prevalence estimates between 3.9% to 7.4% (4-7): two studies focused on Lima (4, 5) but were conducted 10 years ago while the other two recent studies had a better national representation (6, 7). Obesity seems to be the driver of DM in Peru: the Population Attributable Risk (PAR) of obesity for DM was estimated to be 23.9%(7).

It is within this context that these two diseases – TB and DM – collide in Peru, though, there is little evidence regarding the association between TB and DM in our setting. One study reported a DM prevalence of 11% among TB patients with high risk of MDR-TB (8); however, DM was defined using medical records, so this result may be an underestimate. A small cohort study found a delay in culture conversion among TB patients with DM compared with TB patients without DM, but the sample size was small and DM was defined only by clinical records(9). Another study showed that DM history was associated with mortality among MDR-TB patients in Lima(10). However, as in the previous study, the DM definition was mostly based on medical records, so there is a risk of misclassification of DM exposure.

Considering the lack of information about DM prevalence among TB patients in Peru, the main objective of this study is to evaluate the prevalence of DM and its associated factors among Peruvian TB patients in TB clinics at 4 Primary Health Centers across Lima.

Materials and Methods

Study design and Study Population

This was a cross-sectional study conducted in 4 Primary Health Centers in Lima, Peru from January 2014 to November 2015. Patients were enrolled at TB diagnosis and before initiation of TB treatment. This cross-sectional analysis is part of the activities of the TANDEM Consortium (www.tandem-fp7.eu). TANDEM is a multi-site project whose main objective is to provide evidence regarding the association of TB and DM(11). We included patients recently diagnosed with Pulmonary TB who were older than 18 years old and who had provided a blood sample for HbA1c and blood glucose. For this cross-sectional analysis, the minimum sample size calculated (considering a significance level of 5%, a prevalence of 7%, and precision 2.5%) was 401.

Study definitions

We defined individuals with pulmonary TB as any individual who initiated treatment at a Directly-Observed Therapy–Short Course (DOTS) clinic, as per the Peruvian National TB Guidelines(12). We defined DM as a HbA1c higher than 6.5% and/or having a previous DM diagnosis. All participants were tested for HbA1c as per World Health Organization (WHO) recommendations for DM screening(13, 14), regardless of their previous DM status. A study in Peru showed that the use of HbA1c compared with Fasting Blood Glucose (FBG) detected more DM cases(15). Pre-diabetes was defined as a HbA1c value between 5.7% and 6.4%(16). Body Mass Index (BMI) and Waist-to-Hip Ratio (WHR) were measured as a proxy for obesity: underweight was defined as BMI≤18.5kg/m^2, normal weight a BMI between 18.5kg/m^2 to 25kg/m^2, overweight a BMI>25kg/m^2, and obese higher than 30kg/m^2. Socio Economic Status (SES) was calculated using an index based on the approach proposed by Vyas & Kumaranayake(17). This SES index classified the study population from the poorest to the richest using quintiles, using Principal Component Analysis (PCA) in household characteristics, access to utilities and ownerships in absence of income and/or expenditure measurements, which usually are linked with recall bias, seasonality and other problems related with the data collection.

Data analysis

We used REDCap 6.9.1(18) for data collection and management, and STATA 13.0 (StataCorp, Texas, USA) for statistical analysis. Categorical variables were presented with their frequencies and continuous variables were summarized using median and interquartile ranges (IQR). Analyses between groups was done using the Mann-Whitney U test for non-parametric data, and using the chi-squared test for categorical variables. The main analysis used a Poisson regression model with robust variance to estimate crude and adjusted prevalence ratios (19), evaluating factors associated with the presence of DM at TB diagnosis. A sub-analysis was performed with patients over 35 years old using the same approach.

Ethics

This study was approved by the Institutional Review Board (IRB) at the Universidad Peruana Cayetano Heredia with permission from the Peruvian National TB Control Program. TANDEM, as the parent study, also had approval as the TANDEM Coordinating Centre from the IRB at the London School of Hygiene and Tropical Medicine.

Results

669 patients were eligible and 484 (77.8%) were enrolled (Figure 1). We didn't find a statistical difference between those enrolled and those not, and the main reason for refusing to participate was the number blood samples (5 tubes of 8ml). Participant characteristics are listed in Table 3.1. Forty-four (9.1%; 95% CI: 6.8%-12.0%) participants were classified as living with DM; of which 16 (34%) were diagnosed with DM at enrollment, 20 (23%) within less than 1 year prior to enrollment, 11 (25%) within 1-5 years prior and 7 (16%) more than 5 years prior to enrollment. The median age among TB patients with DM was 51 years (IQR: 45.0-58.5) compared to 28.5 years (IQR: 22.0-40.0) among those without DM. DM prevalence among TB patients older than 35 years was 18.1% (95%CI: 13.5%-23.8%) in this age group compared to 1.9%

(95%CI: 0.8%-4.4%) among TB patients < 35 years of age. Only nine TB patients (1.9%) were HIV positive, of which only one was also diagnosed with DM. The median BMI among TB patients with DM was 24.6kg/m^2(IQR: 21.7-27.5) compared to 21.8kg/m^2(IQR: 19.8-24.0) among patients without DM. Almost half (47.7%) of the participants with DM were overweight or obese, compared with 17.4% among TB non-DM (p<0.05). Among TB patients with DM, 10 (22.7%) had a previous TB episode compared to 139 (31.6%) among patients without DM (p=0.23).

Regarding pre-diabetes, the prevalence in the study population was 25.6% (95%CI: 21.9%-29.7%) and among participants over 35 years old was 27.3% (95%CI: 21.8%-33.7%). Among TB patients with pre-diabetes, 48 (38.7) had a previous TB episode, a higher percentage compared with TB-DM and TB non DM (91 participants, 28.8%); median Body Mass Index (BMI) was 21.6 (IQR: 19.7-23.6), median HbA1c was 5.8% (IQR:5.7-6) and median Waist-Hip Ratio (WHR) was 0.89 (IQR:0.84-0.93), showing a higher BMI and WHR in participants with pre-diabetes compared with non-DM participants.

Crude and adjusted regression analysis using a Poisson Regression model with robust variance are shown in Table 3.2. Age and a BMI higher than 30kg/m^2 were associated with DM in the adjusted analysis. In Table 3.3, we can observe only age over 65, previous TB episode and a smear positive result was associated with pre-diabetes compared with TB non-DM participants.

We conducted a sub-analysis in the population over 35 years of age. Median HbA1c was 5.6% (IQR: 5.3-6.0), median BMI was 25.6 kg/m^2 (IQR:20.4-25.6) and median WHR was 0.90 (IQR: 0.87-0.95). We display the crude and adjusted regression analyses for participants over 35 years old in Table 3.4. The factors associated with TB-DM among this age group were age and a BMI higher than 30kg/m^2.

Discussion

Our results show a high DM prevalence among TB patients (9.1%), particularly in patients older than 35 years of age (18.1%). These results are higher than the national estimates (around 6% and 7% of DM prevalence in people over 35 years and over 25 years respectively)(6, 7).

Regarding age, several studies have shown that age is an important factor associated with DM among TB patients (20-26), consistent with our results. DM is more prevalent in older people (16, 27); however, in recent years, the mean age of individuals with DM has been decreasing and individuals with DM are increasingly younger (3). Thus, there is an increasingly greater age overlap between populations with DM and TB, given that younger individuals are generally at greater risk for TB (28).

Almost 50% of TB-DM participants knew about their DM status at least 5 years before their TB diagnosis. Considering that DM increases the risk of active TB (29), interventions to prevent TB within DM populations, especially in areas with high TB prevalence, are urgently needed. These interventions are especially needed in Peru, where the prevalence of latent TB, although unknown, is likely high given that in similar settings such as Mexico the prevalence of latent TB is around 50% (30). These interventions should include intense glucose control, because most of our TB-DM patients had uncontrolled glucose (median HbA1c 10.3% with extreme values of 17%) and a history of irregular adherence to medication and medical control. Furthermore, there are studies showing the association of poor glycemic control with worse TB treatment outcomes(8, 31, 32).

Obesity was also associated with DM among this TB population and there are other studies confirming our findings of an association of higher BMI with DM(22, 33, 34) among TB patients. Active TB is well known to be associated with under-nutrition (35, 36), and this nutritional condition increase the mortality among TB patients(37). Also, some studies showed the role of overweight/obesity (based on BMI) as a protector factor

for active TB(38, 39), and overweight/obese TB patients had lower risk for mortality compared with TB patients with undernutrition(37). Overweight and obese patients have differences in immune response, basically through adipose tissue(40): for example adypocytokine (cytokines produced by adipose tissue) plasma levels are altered in TB-DM patients compared with TB non-DM patients, revealing a potential role of inflammatory status in TB-DM patients(41). Furthermore, Leptin (a hormone related with appetite), which is usually higher in obese patients, inducing pro-inflammatory cytokines and Th1 response(40) is also altered in TB-DM patients, who were reported to have lower plasma levels of leptine compared TB non-DM patients, but both have a negative correlation between leptin levels and BMI(42). However, not all this evidence is conclusive (leptin levels can be affected by multiple factors, such as diet)(43) and further research is required.

A recent study in 3 provinces in Peru with the aim to evaluate modifiable risk factors for hypertension and DM, showed a pre-diabetes prevalence of 18%(7), lower than our study, leading us to hypothesize that TB participants potentially have a higher risk of developing DM in the following years. However, the definition of pre-diabetes needs to be considered carefully, since infections can produce hyperglycemia in general(44, 45) and TB infections are also known to cause transient hyperglycemia (46-48). The definition of pre-diabetes *per se* is under scrutiny because there is evidence showing that more than half of persons with pre-diabetes don't develop diabetes after 10 years(49); thus, the use of the standard definition of pre-diabetes can lead to over-diagnosis and overmedication(50, 51), increasing potential unnecessary risks (stress, drugs adverse events) in a vulnerable population such as those with TB. A study in Tanzania showed that the glucose levels reduced after TB treatment finished(48), but also showed the association of hyperglycemia with bad TB treatment outcomes (death or treatment failure), so a suggestion based in this evidence should be a confirmatory glucose test after TB treatment finish for patients with hyperglycemia (pre-diabetes or newly DM diagnosed) to confirm as a case of DM or as a case of transient hyperglycemia.

This study, like any observational study, has limitations. First, not all eligible participants were possible to enroll in the study (77.8% among eligible were enrolled, described in Figure 1), while only 4 TB-DM were not enrolled. Possible reasons why these patients chose not to participate in our study are lack of time, fear of blood draw or receiving DOTS after clinic attention time. This issue can make our DM prevalence result overestimated, however, the population who wasn't enrolled are similar in age (mean age 29.4 years; SD: 12.8) and gender (60%) distribution with the study participants, so we don't expect a huge difference in the estimate. A second limitation is the small number of TB-DM individuals (n=44): some factors that we would expect to be associated with TB-DM, such as smoking status(31, 52, 53), were not associated with TB-DM in our study population (none of our TB-DM participants has history of smoking). This unexpected result may be due to chance, with the small sample size leading to a lack of statistical power and also can be explained by the low prevalence of smoking among TB patients: a similar population in Lima (n=2131) reported around 97% of TB patient didn't smoke(54).

Nevertheless, our study has strengths: all patients were screened for DM with HbA1c, a standardized and validated measure, so the risk of DM misclassification is lower in our study population. Secondly, while not necessarily representative of all individuals with TB in Peru, many areas in Lima (where the majority of TB patients live) are very similar in demographics and socio-economic characteristics as in our study sites, so we do not expect that our results would differ greatly in other parts of the city.

WHO and the UNION (International Union Against Tuberculosis and Lung Diseases) recommend bi-directional screening for TB and DM in the last years (55, 56). Preliminary results in Peru in 600 DM patients screened for TB, showed that only one patient had active TB(57), however, when DM is screened among TB patients, our study showed a higher frequency of the comorbidity, specially in people over 35 years. The Peruvian National TB program uses Fasting Blood Glucose (FBG) for DM screening, but, a study in Peruvian population showed the use of HbA1c diagnosed more DM cases than FBG, specifically in low-income population (such as TB population)(15). So, in the

Peruvian context, our recommendation based in these results and other local evidence is the implementation of HbA1c test for DM screening, specially for people over 35 years old and with BMI higher than 25kg/m^2.

In conclusion, TB-DM was associated with age and obesity, and more than 30% of the patients evaluated had hyperglycemia. Further studies exploring the role of age, obesity and the role in transient hyperglycemia in TB patients and its association with DM are needed.

Tables

Table 3.1: Participant characteristics

Characteristics	Total (n=484)	TB non-DM (n=440)	TB-DM (n=44)	P-value
Median age (IQR)	31 (23-44)	28.5 (22-40)	51 (45-58.5)	< 0.05
Older 35 years old (%)	216 (44.6%)	177 (40.2%)	39 (88.6%)	< 0.05
Male (%)	279 (57.6%)	256 (58.2%)	23 (52.3%)	0.45
Median BMI kg/m^2 (IQR)	22.0 (19.9-24.4)	21.8 (19.8-24.0)	24.6 (21.7-27.5)	< 0.05
Median Waist-to-Hip Ratio (IQR)	0.88 (0.84-0.93)	0.88 (0.83-0.92)	0.96 (0.89-0.97)	< 0.05
Median HbA1c % (IQR)	5.5 (5.2-5.8)	5.4 (5.2-5.7)	10.3 (8-12.7)	< 0.05
Median Random Blood Glucose (IQR) mg/dl	97.2 (84.6-115.2)	95.4 (84.6-111.6)	196.2 (119.9-249.8)	< 0.05
Quintiles SES (%)*				0.14
Q1: Poorest	135 (29.6%)	126 (30.4%)	9 (21.4%)	
Q2: Poor	97 (21.3%)	90 (21.7%)	7 (16.7%)	
Q3: Middle income	83 (18.2%)	70 (16.9%)	13 (31.0%)	
Q4: Upper middle income	76 (16.7%)	71 (17.2%)	5 (11.9%)	
Q5: Richest	65 (14.3%)	57 (13.8%)	8 (19.1%)	
Smear Result (%)				0.10
Negative	168 (34.7%)	158 (35.9%)	10 (22.7%)	
Scanty	52 (10.7%)	49 (11.1%)	3 (6.8%)	
1+	88 (18.2%)	76 (17.3%)	12 (27.3%)	
2+	114 (23.6%)	99 (22.5%)	15 (34.1%)	
3+	62 (12.8%)	58 (13.2%)	4 (9.1%)	
Previous TB Episode (%)	149 (30.8%)	139 (31.6%)	10 (22.7%)	0.22
Coughing more 14 days (%)	413 (85.3%)	375 (85.2%)	38 (86.4%)	0.84
Ever smoke (%)	45 (9.3%)	45 (9.3%)	0 (0%)	0.03
Family history of DM (%)	76 (15.7%)	60 (13.6%)	16 (36.4%)	<0.01

*n=456

Table 3.2: Factors associated with DM among TB patients

Factors	Crude PR (95%CI)	P-value	Adjusted PR (95%CI)	P-value
Age				
18-35 years	REF		REF	
35-45 years	3.4 (1.0-10.7)	0.04	3.5 (1.0-12.3)	0.05
45-55 years	16.4 (6.3-42.3)	<0.05	15.6 (5.2-47.1)	<0.05
55-65 years	17.3 (6.3-47.4)	<0.05	14.4 (4.1-50.5)	<0.05
>65 years	8.9 (2.7-29.1)	<0.05	7.9 (2.1-29.9)	<0.05
Male	0.8 (0.5-1.4)	0.5		
SES				
Q1	REF		REF	
Q2	1.1 (0.4-2,8)	0.87	0.8 (0.3-2.0)	0.60
Q3	2.3 (1.0-5.3)	0.04	0.9 (0.4-2.1)	0.86
Q4	0.9 (0.3-2.8)	0.98	0.5 (0.2-1.4)	0.16
Q5	1.8 (0.7-4.6)	0.19	1.0 (0.4-2.5)	0.82
Smear result Positive	1.8 (0.9-3.6)	0.09		
Previous TB Episode	0.7 (0.3-1.3)	0.2		
BMI				
Normal	REF		REF	
Underweight	1.2 (0.4-3.4)	0.75	1.1 (0.4-3.4)	0.85
Overweight	3.1 (1.7-5.9)	<0.05	1.9 (1.0-3.7)	0.06
Obese	6.9 (3.2-14.7)	<0.05	2.7 (1.3-5.7)	0.01
Family history of DM	3.1 (1.7-5.4)	<0.05	1.6 (0.9-2.9)	0.13

Table 3.3: Factors associated with pre-diabetes compared with non-DM TB patients

Factors	Crude PR (95%CI)	P-value	Adjusted PR (95%CI)	P-value
Age				
18-35 years	REF		REF	
35-45 years	1.1 (0.8-1.7)	0.6	1.1 (0.7-1.6)	0.8
45-55 years	1.3 (0.8-2.1)	0.3	1.3 (0.8-2.1)	0.4
55-65 years	1.2 (0.6-2.3)	0.7	1.1 (0.6-2.2)	0.7
>65 years	2.4 (1.7-3.6)	<0.05	2.5 (1.7-3.6)	<0.05
Male	1.1 (0.8-1.4)	0.7		
SES				
Q1	REF			
Q2	1.1 (0.8-1.7)	0.5		
Q3	0.8 (0.5-1.4)	0.5		
Q4	0.8 (0.5-1.3)	0.3		
Q5	1.3 (0.9-2.0)	0.2		
Smear result positive	1.6 (1.1-2.3)	<0.05	1.7 (1.2-2.3)	0.04
Previous TB Episode	1.4 (1.0-1.8)	0.04	1.3 (0.9-1.8)	0.06
BMI				
Normal	REF			
Underweight	0.9 (0.5-1.4)	0.6		
Overweight	1.0 (0.7-1.5)	0.9		
Obese	1.6 (0.7-3.4)	0.2		
Family history of DM	1.0 (0.7-1.6)	0.9		

Table 3.4: Factors associated with DM among TB patients over 35 years' old

Factors	Crude PR (95%CI)	P-value	Adjusted PR (95%CI)	P-value
Age				
35-45 years	REF		REF	
45-55 years	4.8 (2.0-11.4)	<0.05	4.5 (1.9-10.6)	<0.05
55-65 years	5.2 (2.0-13.1)	<0.05	4.5 (1.7-11.9)	<0.05
>65 years	2.8 (0.9-8.4)	0.07	3.0 (1.0-9.0)	0.05
Male	0.8 (0.5-1.4)	0.43		
SES				
Q1	REF			
Q2	0.7 (0.3-2.1)	0.60		
Q3	1.8 (0.8-4.1)	0.17		
Q4	0.6 (0.2-2.0)	0.45		
Q5	1.9 (0.8-4.7)	0.16		
Smear result Positive	1.5 (0.7-2.8)	0.3		
Previous TB Episode	0.6 (0.3-1.1)	0.09		
BMI				
Normal	REF		REF	
Underweight	0.6 (0.1-2.4)	0.47	0.5 (0.1-2.2)	0.37
Overweight	1.6 (0.8-3.1)	0.14	1.4 (0.8-2.6)	0.30
Obese	3.7 (1.9-7.4)	<0.05	2.6 (1.3-5.3)	< 0.05
Family history of DM	1.8 (1.0-3.3)	0.04	1.4 (0.8-2.5)	0.22

Figures

Figure 3.1: Flowchart of participants' enrollment

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                    ┌─────────────────┐
                    │  622 Eligible TB│
                    │    Patients     │
                    └─────────────────┘
                             │
                             │           ┌──────────────────────────────────┐
                             │           │ Not enrolled:                    │
                             │           │   • 138 patients (60%  Male,     │
                             ├──────────▶│     40% Female)                  │
                             │           │   • 134 non TB-DM                │
                             │           │   • 4 TB-DM: 3 Male, 1 Female    │
                             │           └──────────────────────────────────┘
                             ▼
                    ┌─────────────────┐
                    │  484 Enrolled   │
                    │   TB Patients   │
                    └─────────────────┘
                      ╱           ╲
                     ╱             ╲
                    ▼               ▼
          ┌──────────────────┐  ┌──────────────────┐
          │  440 TB non-DM   │  │    44 TB-DM      │
          └──────────────────┘  └──────────────────┘
```
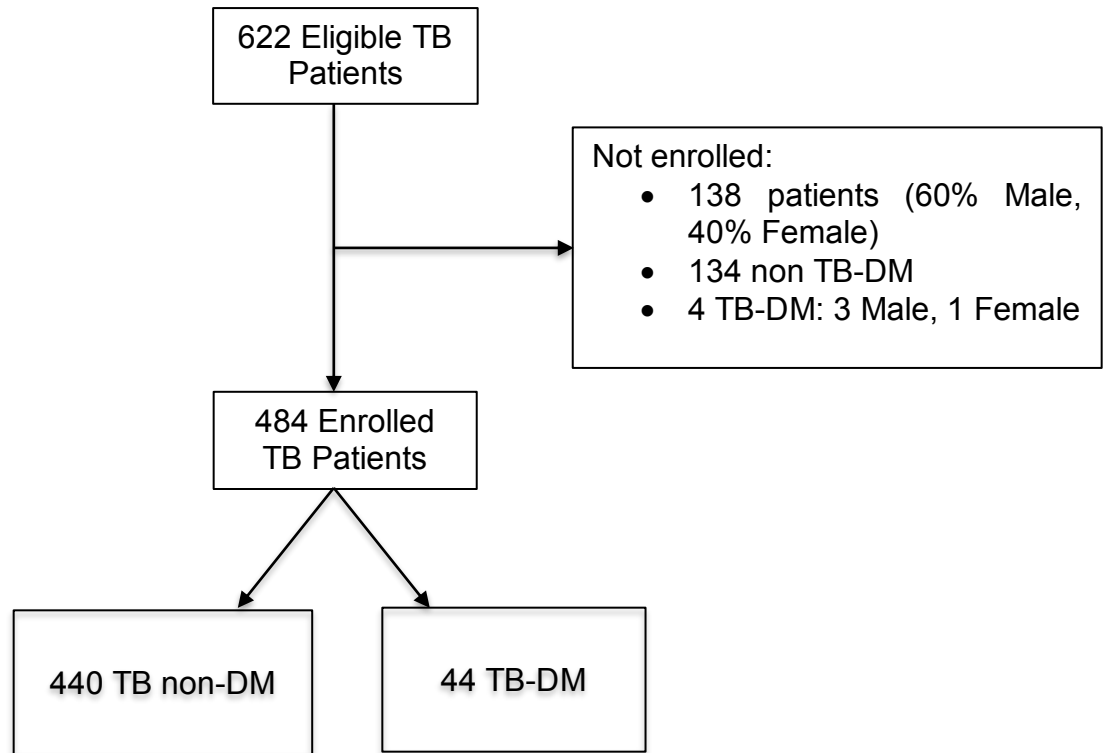
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4. <u>Chapter Four: Paper III</u>

Mortality among Peruvian Multidrug Resistant Tuberculosis patients with and without Diabetes

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Summary

Setting

Lima, Perú

Objective

To compare TB treatment outcomes among MDR-TB patients with and without DM.

Design

MDR-TB records from the operational patient's database of Peru's National TB Program were reviewed. Adult patients who started MDR-TB treatment between 2010-2013 in Lima were included in the study. Cox regression was used to estimate crude and adjusted Hazard Ratios, evaluating factors associated with mortality.

Results

1999 adult MDR-TB patients started treatment between 2010-2013, 64.8% were male. The median age was 27 (IQR: 22-37) and 28.7% were over 35 years old. Median BMI was 21.8kg/m^2 (IQR: 19.5-24.0), 19.3% had a BMI>25kg/m^2, median blood glucose level 85.8mg/dl (IQR: 77-96) and HIV prevalence was 3.4%. The overall prevalence of DM among MDR-TB was 6.4% (95%CI: 5.4%-7.6%). Being older than 35 years old, BMI>25kg/m^2 and glucose≥200mg/dl were all associated with DM among MDR-TB patients (p-value<0.05). Mortality was higher among MDR-TB patients with DM (19.5%) compared to patients without DM (7.1%) and after adjustment for several confounding factors, MDR-TB patients with DM were three times as likely to die (aHR=2.9 95%CI:1.4-5.9; p-value< 0.05).

Conclusions

MDR-TB patients with DM have greater mortality than those without DM, and are generally older, more overweight/obese and tend to have higher mortality risk compared with MDR-TB patients without DM.

Keywords: Tuberculosis, MDR, Diabetes, Mortality

Introduction

Multidrug Resistant Tuberculosis (MDR-TB) is a big threat for TB control, especially in low-and-middle income countries (LMICs). Almost half millions of TB patients had MDR-TB worldwide and almost 10% of them had XDR-TB (Extensively drug-resistant TB) in 2015(1). Peru is one of the Latin America countries with the highest burden of MDR-TB, with almost 30% of estimated MDR-TB cases in the Americas in 2015(1) and the prevalence of MDR-TB among new and previously TB cases with 5.3% and 20% respectively. Diabetes (DM) prevalence is increasing worldwide in recent years (9.1% in 2015), but specifically in low-and-middle income countries (LMICs)(2), and the national prevalence in Peru is around 7%(3). There is an increasing risk of infections (such as TB) if DM patients lack adequate glucose control (4), and in settings such as Peru there is a lack of good glucose control(5). The risk of not reducing the rise of DM prevalence could be to not reach TB control goals by 2035 as is showed by a mathematical model, delaying TB control goals (6). The association between TB-DM showed a higher risk for bad TB treatment outcomes(7). Furthermore, people living with HIV have higher risk for TB, however the population at risk is higher among DM, with Population attributable fraction (PAF) between 15-25, compared with HIV (PAF=12)(8).

Among the multiple risk factors associated with MDR-TB, one important risk factor is DM(9-11). The DM prevalence among MDR-TB patients is ranges from 10%-60%(9, 10) and the odds of having MDR-TB among DM patients is almost 2 times compared with non-DM patients(12, 13). The clinical presentation of MDR-TB among patients with DM were reported as more severe: there is evidence of the association of primary MDR-TB and DM, increasing the time for sputum culture conversions(14, 15), and also the extension of lung damage seems to be bigger than sensitive TB(16). Studies reported that MDR-TB patients with DM are usually older (over 35 years old) and have a higher Body Mass Index (BMI) compared with non-DM patients (16, 17).

Due the lack of evidence of treatment outcomes among MDR-TB Peruvian patients and its association with DM, we analyzed a cohort of MDR-TB patients in Lima-Peru

between 2010-2013, to determine the DM prevalence and factors associated with MDR-TB treatment outcomes among MDR-TB patients, specifically with mortality.

Methods

Setting and Study Design

We performed a retrospective cohort study using the operational MDR-TB database from the Peruvian National TB Program. This database registers all Peruvian MDR-TB cases and links with electronic clinical TB records, which includes demographic information, anthropometric measures, TB information (bacteriological and drug sensitivity results), comorbidities (HIV and DM) and TB treatment outcomes.

Population

Adult patients (older than 18 years old) who started MDR-TB treatment between January 2010 and December 2013 in Lima were included in the study. We consider only the first episode of MDR-TB registered during the study period and its treatment outcome.

Study definitions

All participants were defined as a MDR-TB case. MDR-TB diagnosis (based in DST of isoniazid and rifampicin) was the same for all patients and used DST techniques. Diabetes was routinely requested for screening to all MDR-TB patients as a part of baseline laboratory test (fasting blood glucose), and DM diagnoses were abstracted from the patients' medical records. TB treatment outcomes were categorized according to WHO guidelines: cure, treatment completed, default, death and treatment failure.(18). Our primary outcomes were 1) death and 2) a composite bad treatment outcome (BTO) consisting of death, default or treatment failure.

Statistical Analyses

We used STATA 13.0 (StataCorp, Texas, USA) for all analyses. Continuous variables were summarized using median and interquartile ranges (IQR), and categorical variables were summarized using frequencies. Analyses between groups were done using the

Mann-Whitney U test for non-parametric data, and using Chi-squared test for categorical variables. The log-rank test was used to compare Kaplan-Meier survival curves. Cox regression model was used to estimate crude and adjusted Hazard Ratios, evaluating factors associated with mortality among MDR-TB patients. The proportional hazard assumptions were checked using Schoenfeld residuals.

Because this dataset is an operational National TB program database, there are missing values of some variables. The frequency of missing values was higher than 10% but under 20% for BMI$\geq$25kg/m^2 (17.5%) and DST result for pyrazinamide and ethambutol resistance (19.3%), we did multiple imputation of missing variables using regression models with a multivariate normal distribution (MVN) imputation procedure, under the assumption that these variables were missing at random (MAR)(19).

Institutional Review Board Approval

The dataset was de-identified before analysis to protect the confidentiality of the patients. This study had approval from the IRB at Universidad Peruana Cayetano Heredia.

Results

Baseline characteristics

1999 MDR-TB adult patients were started treatment during the study period and were included in this analysis. The median age of these patients was 27 years (IQR: 22-37) and 1296 (64.8%) were male. DM prevalence was 6.4% (95%CI 5.4%-7.6%). MDR-TB patients with DM were older (median 52 years vs 26 years) and had higher BMI (median 23.0kg/m^2 vs 21.6 kg/m^2) compared with MDR-TB patients without DM (Table 4.1). Frequency of having a prior episode of TB was similar between groups (6.1% vs 6.3%), and the median number of previous TB treatments was 1 for both groups (Table 4.1). Patients with DM (1.6%) had lower HIV prevalence compared to those without DM (3.5%).

MDR-TB treatment outcomes and mortality

During MDR-TB treatment, 158 (7.9%) deaths occurred, 25 (19.5%) among patients with diabetes compared to 133 (7.1%) among patients without DM (p=0.05) (Figure 4.1). Regarding BTO, there was not difference between patients with and without DM (36.0% vs. 40.6%; p-value: 0.3) (Table 4.2). After adjustment for age, sex, BMI, inmate status, HIV, previous TB treatment, positive AFB smear at beginning of treatment, RBG over 200mg/dl and full resistance to 1st line of TB drugs (isoniazid, rifampicin, ethambutol and pyrazinamide), patients with DM had 2.9 times the hazard for death compared with patients without DM (adjusted Hazard Ratio aHR: 2.9; 95%CI 1.4-5.9) (Table 4.3).

Because BMI and DST result for ethambutol and pyrazinamide had missing data, we did a MVN imputation procedure (Appendix Table 4.1 and Appendix Table 4.2). Almost all of the associations remained similar, with the exception of full resistant for 1st line of TB drugs, which became non-significant in the imputed model.

Discussion

Mortality was higher among MDR-TB patients with DM compared with non-DM patients (19.5% vs 7.9%). MDR-TB patients with DM were older and had a higher median BMI compared with MDR-TB without DM in our study population. Our findings show that bad treatment outcomes frequency was similar among DM and non-DM patients. Also, we found that DM prevalence among MDR-TB patients over 35 years old was higher than the DM prevalence reported in the general adult Peruvian population (19.9% vs 7.0%)(3), showing DM as a more common comorbidity than HIV in this population. These findings provide evidence of the urgent necessity to implement a comprehensive approach for MDR-TB and DM management, considering the increasing prevalence of DM in LMICs settings including Peru and the increased risk of mortality in these patients.

An increased risk for negative TB treatment outcomes has been reported in patients with TB-DM in several studies(20-23). A meta-analysis showed a Risk Ratio (RR) of 1.7 (95% CI:1.4-2.1) for bad treatment outcomes and 1.9 (95% CI:1.5-2.4) for death among TB-DM patients compared with TB without DM (7). Also, compared patients with drug-susceptible TB, MDR-TB patients have been reported to have higher mortality risk and this mortality was associated with DM, HIV, lower education and number of previous TB episodes(24).

Our findings are similar to results presented by other studies on MDR-TB and TB in different settings. One study in Korea(21) found similar characteristics (older age and higher BMI) and higher risk of death among MDR-TB patients with DM; however, they found higher risk for treatment failure, which we did not find. One explanation can be the difference in treatment successful rate: in our cohort was 63.7% overall, higher compared with Korea (45.3%).) Studies in Egypt and China reported DM as a risk factor for unsuccessful treatment outcome (defined as default, death and treatment failure)(25)(26).

The role of glucose in MDR-TB and TB in general is not well understood. People with poor glucose control have a higher risk of developing active TB (27) and a higher risk for poor treatment outcomes(28, 29). DM patients had an impaired immune system (innate and adaptive immunity)(30, 31), affecting host's response against *M. tuberculosis*, with a lower interaction between monocytes and *M. tuberculosis* in TB-DM patients with poor glucose control(32). Similar results were found in other infections, where glucose control plays an important role in infection control among DM patients(4). Severe TB also appears to be more common among DM patients with uncontrolled glucose (HbA1c≥7%) compared with DM patients with good glucose control (HbA1c<7%), presenting more lung cavities and longer time for culture conversion(33) and poor treatment response(34). Unfortunately, our database didn't have a complete record of chest X-ray (only 58.5% of the patients had x-ray data), showing that there was not difference between patients with DM compared with patients without DM. Also, time to culture conversion was not routinely recorded, and HbA1c testing was not routine in this population. This inadequate glucose monitoring unfortunately is very common among DM patients in Peru, mainly because the inability of Peruvian health system to provide adequate glucose monitoring and DM care for DM patients)(35, 36).

Hyperglycemia is common in several infections(37). Regarding TB, a study in Tanzania evaluated hyperglycemia at TB diagnosis and the glucose level at the beginning and end of TB treatment comparing with non-TB controls and found in many cases hyperglycemia was transient, disappearing after TB treatment ends, however, hyperglycemia was associated with poor TB treatment outcomes(38). To reduce the potential DM misclassification, a confirmatory DM test should be done after the completion of MDR-TB treatment.

TB treatment is also affected by DM: there are changes in pharmacokinetics (specifically in rifampicin) among TB with DM patients compared with TB without DM patients, with a lower Area-under-curve (AUC) between 0-6 hours(39). We did not find pharmacokinetics studies evaluating 2^{nd} line drugs for MDR-TB patients, however studies on DM and other infectious diseases showed a difference in antibiotic absorption,

associated with impaired renal function(40). Renal function in DM patients is affected by glucose control and high BMI, affecting one 2nd line drug type (for example aminoglycosides), this is why it is necessary to adjust the doses of this drug among DM patients(40, 41).

This study has limitations. The database is from the operational MDR-TB national database, thus has a high risk of information bias. Many key variables were complete (DM status, treatment outcome, age, gender), but others have missing data (HIV, BMI, chest X-rays, DST results). Nevertheless, after handling missing data with multiple imputation, we observed very similar measures of association, suggesting a similar strength and direction of the association. Other unmeasured confounders known to be associated with TB outcomes, such as HbA1c (due its higher cost and low availability at health centers in Lima), renal function tests (creatinine), smoking status, alcohol consumption and DM comorbidities, were not routinely recorded in this cohort, however many of these confounders are now registered in the National TB Register, and can be used to improve clinical management and support.

Our study also has several strengths. First, we were able to evaluate all the population with MDR-TB diagnosis in Lima during the study period, reducing the risk of selection bias; also; additionally, treatment outcomes were recorded for all study patients, making our results a good approximation of the reality of MDR-TB in Lima during the study period. DM status was routinely tested as a part of baseline laboratory tests (fasting glucose) for all MDR-TB patients and was abstracted from clinical records for this study, so this reduce the risk of underestimation of DM prevalence.

Testing for DM and recording DM status for TB patients should be universal for this population: Our results in addition with other evidence (42) show the necessity of a comprehensive approach for DM diagnosis and management for TB and MDR-TB patients, including the implementation of HbA1c test at TB clinics, with the aim to improve glucose monitoring and DM diagnosis and control.

In conclusion, our study showed a higher prevalence of DM among MDR-TB patients over 35 years old and the association of DM status with higher risk of mortality among MDR-TB. Further studies are necessary to evaluate the role of glucose control among MDR-TB patients with DM in addition with research in the interaction between MDR-TB treatment and DM management and therapy with the aim to improve MDR-TB treatment outcomes. Universalization of glucose tests (including HbA1c) and the implementation of a comprehensive TB-DM care program should be addressed to reach a better management of MDR-TB patients with DM.

Tables

Table 4.1.- Clinical characteristics of MDR-TB patients with and without DM (n=1999)

Characteristics	Total (n=1999)	MDR-TB non-DM (n=1871)	MDR-TB DM (n=128)	p-value
Media Age (IQR)	27 (22-37)	26 (22-34)	52 (44-59)	< 0.05
Age over 35 (%)	574 (28.7%)	460 (24.6%)	114 (89.1%)	<0.05
Male (%)	1296 (64.8%)	1218 (65.1%)	78 (60.9%)	0.3
Median BMI (IQR) (n=1652)	21.8 (19.5-24.0)	21.6 (19.5-23.9)	23.0 (10.7-27.1)	<0.05
BMI $\geq$ 25kg/m^2 (%) (n=1652)	318 (19.3%)	283 (18.3%)	35 (34.7%)	<0.05
Inmate (%)	141 (7.1%)	130 (7.0%)	11 (8.6%)	0.5
HIV positive (n=1930)	65 (3.4%)	63 (3.5%)	2 (1.6%)	0.3
Cavitary disease (%) (n=1169)	461 (39.4%)	432 (39.4%)	29 (40.3%)	0.9
Median number of previous TB treatments	1 (1-2)	1(1-2)	1(1-2)	0.8
$\geq$ 2 previous TB treatments	917 (45.9%)	858 (45.9%)	59 (46.1%)	0.9
Median months on treatment	19 (14-22)	19 (14-22)	20 (14-24.5)	0.08
Positive AFB smear at treatment start	1546 (77.3%)	1440 (77.0%)	106 (82.8%)	0.1
Resistant to Ethambutol and Pirazinamide (n=1614)	459 (28.4%)	429 (28.4%)	30 (29.7%)	0.8
Median glucose mg/dl (IQR) (n=1934)	85.8 (77-96)	85 (76-94)	155.9 (115.4-236)	<0.05
Glucose $\geq$ 200 mg/dl (%) (n=1934)	54 (2.8%)	13 (0.7%)	41 (33.1%)	<0.05

Table 4.2.- Initial treatment outcomes among MDR-TB patients with and without DM (n=1999)

Treatment outcome	Total (n=1999)	MDR-TB non-DM (n=1871)	MDR-TB DM (n=128)	p-value
Cured (%)	880 (44.0%)	830 (44.4%)	50 (39.1%)	0.5
Treatment completed (%)	393 (19.7%)	367 (19.6%)	26 (20.3%)	0.9
Default (%)	514 (25.7%)	493 (26.4%)	21 (16.4%)	0.3
Death (%)	158 (7.9%)	133 (7.1%)	25 (19.5%)	0.05
Treatment failure (%)	54 (2.7%)	48 (2.6%)	6 (4.7%)	0.8
Bad treatment outcome* (%)	726 (36.3%)	674 (36.0%)	52 (40.6%)	0.3

Table 4.3.- Associate factors with mortality among MDR-TB patients (n=1564)

Factors	Crude HR (95% CI)	p-value	Adjusted HR (95%CI)	p-value
DM	2.6 (1.7-4.0)	<0.05	2.9 (1.4-5.9)	<0.05
Age over 35 (%)	2.3 (1.7-3.1)	<0.05	2.1 (1.3-3.3)	<0.05
Male (%)	0.9 (0.7-1.3)	0.6	1.1 (0.7-1.8)	0.6
BMI $\geq$ 25kg/m^2 (%)	0.2 (0.1-0.5)	<0.05	0.2 (0.1-0.5)	<0.05
Inmate (%)	0.9 (0.5-1.7)	0.8	0.7 (0.3-1.5)	0.3
HIV positive	4.4 (2.7-7.2)	<0.05	4.3 (2.3-8.0)	<0.05
$\geq$ 2 previous TB treatments	1.2 (0.8-1.6)	0.4	1.1 (0.7-1.7)	0.6
Positive AFB smear at treatment start	0.8 (0.6-1.2)	0.3	0.7 (0.5-1.1)	0.1
Glucose $\geq$ 200 mg/dl (%)	2.0 (1.0-4.0)	0.06	0.6 (0.2-1.7)	0.3
Resistant to Ethambutol and Pyrazinamide	1.8 (1.3-2.6)	<0.05	2.0 (1.3-3.0)	<0.05

Figures

Figure 4.1.- Kaplan-Meier survival analysis for mortality at 36th months of treatment among MDR-TB patients with and without DM
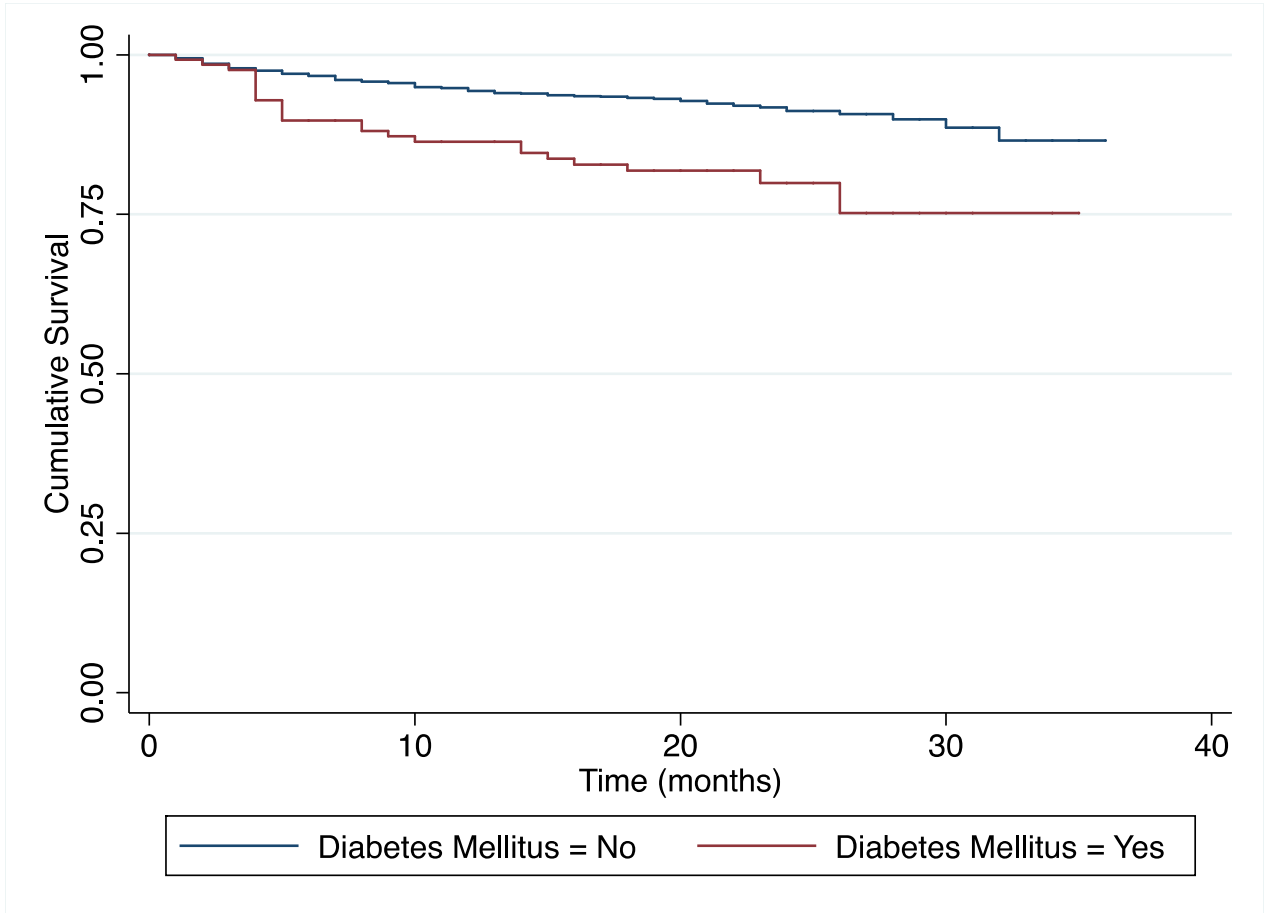
Log-rank test p-value <0.01

Appendix

Appendix Table 4.1.- Full data and Multiple Imputation data

Factors	Full data Coefficient (SE)	p-value	Multiple Imputation Coefficient (SE)	p-value
DM	1.1 (0.4)	<0.05	0.8 (0.3)	<0.05
Age over 35 (%)	0.7 (0.2)	<0.05	0.7 (0.2)	<0.05
Male (%)	0.1 (0.2)	0.6	-0.1 (0.2)	0.6
BMI $\geq$ 25kg/m^2 (%)	-1.5 (0.4)	<0.05	-1.2 (0.3)	<0.05
Inmate (%)	-0.4 (0.4)	0.3	-0.3 (0.3)	0.4
HIV positive	1.5 (0.3)	<0.05	1.3 (0.3)	<0.05
$\geq$ 2 previous TB treatments	0.1 (0.2)	0.6	0.1 (0.2)	0.5
Positive AFB smear at treatment start	-0.3 (0.2)	0.2	-0.2 (0.2)	0.2
Glucose $\geq$ 200 mg/dl (%)	-0.6 (0.6)	0.2	-0.2 (0.4)	0.7
Resistant to Ethambutol and Pyrazinamide	0.7 (0.2)	<0.05	0.4 (0.2)	0.02

SE: Standard Error

Appendix Table 4.2.- Associate factors with mortality among MDR-TB patients using Multiple Imputation dataset

Factors	Adjusted HR (95%CI)	p-value
DM	1.5 (1.3-1.8)	<0.05
Age over 35 (%)	2.2 (2.0-2.4)	<0.05
Male (%)	1.0 (0.9-1.0)	0.3
BMI $\geq$ 25kg/m^2 (%)	0.4 (0.4-0.5)	<0.05
Inmate (%)	0.8 (0.7-1.0)	0.3
HIV positive	3.0 (2.5-3.5)	<0.05
$\geq$ 2 previous TB treatments	1.0 (0.9-1.1)	0.8
Positive AFB smear at treatment start	0.9 (0.8-1.0)	0.2
Glucose $\geq$ 200 mg/dl (%)	1.1 (0.8-1.3)	0.6
Resistant to Ethambutol and Pirazinamide	1.1 (1.0-1.2)	0.2

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5. <u>Chapter Five: Conclusions and Recommendations</u>

<u>*5.1 Summary of Major Findings*</u>

The results discussed in this dissertation highlight the rising importance of DM in TB control, especially in LMICs countries like Peru, where TB control, although started to have a slowly decrease in TB prevalence(1), can be affected by the increasing DM prevalence(2). Despite the evidence of the DM effect in TB clinical presentation, and its association with poor TB treatment outcomes was reported several years ago(3-7), there are still questions to solve and gaps in the evidence to fill.

In Peru, as one of the countries with high burden of TB in Latin America and with the higher number of cases of MDR-TB in the region(1), comorbidities such as DM can put in risk any potential strategy to control. The lack of a strong health system, which affect not only TB program, but also DM programs, make complex the approach for a comprehensive management of TB-DM comorbidity. Most of the results presented here, even though are based in Peruvian population, provide a good approach of DM situation in a LMIC, providing evidence that can help (and in some cases extrapolate) in other settings similar as Peru.

These results in first place, despite the increasing number of publication on TB-DM in the last years, the methodological quality of these studies are no totally adequate and can prone to biased results. Secondly, describe a clear figure of high DM prevalence among TB patients over 35 years old with higher levels of HbA1c (a proxy of poor DM care and glucose management). Third, this dissertation showed DM is a more frequent comorbidity for TB patients than HIV. Fourthly, and last, mortality in MDR-TB patients with DM is frequent and should be observed in detail in this population, with the aim to reduce it.

<u>*5.1.1. Paper I*</u>

Paper 1 showed, after a very wide and comprehensive search (with more than 16000 hits to screen from 4 references databases and more than 300 papers reviewed in full) and the meta-analysis of 11 papers, in countries with double burden of TB & DM, TB-DM patients had higher risk for death compared with TB non-DM patients (2.5 times higher), and when poor TB treatment outcome is evaluated, the risk is 2.6 times higher among TB-DM patients compare with TB non-DM patients. These results confirm previous systematic review(8), which was done mainly with primary studies from high-income countries. Furthermore, the measure of association is stronger in our review compared with the previous one(8), suggesting a stronger association in settings with several problems regarding TB & DM and dealing with structural problems in their health systems.

A sensitivity analysis was done only in studies with prospective glucose test to confirm DM status, reducing the risk of DM misclassification, and the results remained similar (pRR for Death was 2.5 and the pRR for poor TB treatment outcome was 2.5), confirming our previous results. Regarding limitations, there is low risk for publication bias based on the funnel plot, however this study has limitations on the poor quality of the studies and inadequate analysis (due the lack of confounding control)(9).

5.1.2. Paper II

Our results showed a DM prevalence among TB patients of 9.1%, but this prevalence doubles (18.1%) in patients older than 35 years of age. Compared with studies in general population in Peru(10, 11), our results showed a higher prevalence of DM among TB patients. Compared with HIV, DM seems to be a more frequent comorbidity among TB patients (9.1% vs 1.9%).

These results are consistent with the evidence that we found in the literature: TB-DM patients have as common associate factors older age, higher BMI and higher HbA1c. In our case, the median BMI was almost 25kg/m^2 and the median HIbA1c was 10.3%, reflecting a population with overweight (in a population such as TB patient who are

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usually underweight) and with higher levels of glucose (reflecting a chronic poor glucose control).

Another interesting finding is the important percentage (around 26%) of TB patients with high levels of glucose (defined as pre-diabetes: HbA1c values between 5.7%-6.4%). This levels of glucose can be explained by the frequent hyperglycemic status occurred in infection, and specifically in TB patients, who apparently have transient hyperglycemia, with lower glucose levels at the end of TB treatment. However, a study in Tanzania showed an association between these high levels of glucose with poor TB treatment outcome(12), reason why our results, showing a high frequency of hyperglycemic TB patients, should alert to the TB care team to observe closely these patients with the aim to reduce the risk of poor TB treatment outcomes.

5.1.3. Paper III

MDR-TB (one of the biggest threats for TB control in Peru) and its association with DM was discussed in Paper 3. This study, with a cohort of almost 2000 patients, including all MDR-TB patients in Lima between 2010 to 2013, had the aim to evaluate TB treatment outcomes. The findings showed similar epidemiological patterns observed in Paper 2: MDR-TB patients with DM were older and heavier (almost 35% of MDR-TB patients with DM were overweight or obese) compared with MDR-TB patients without DM. The prevalence of DM among this population was almost 7%, however, when the prevalence of DM is restricted for MDR-TB patients over 35 years old, almost 20% of them had DM.

Regardless our results didn't find a difference in poor TB treatment outcomes among MDR-TB patients with DM and MDR-TB patients without DM, the frequency of mortality among MDR-TB patients with DM was much higher compared with MDR-TB patients without DM (19.5% vs 7.9%). Also, DM prevalence among MDR-TB patients was higher than HIV prevalence (3.4%), making DM a more frequent comorbidity among MDR-TB patients with a higher risk for death (aHR=2.9). Despite the logical limitations

that usually appear in studies as the one conducted (using an operational dataset), since the study include all the population available, is a very good description of the DM situation among this MDR-TB population, and alert to the TB health workers to pay attention in MDR-TB patients with DM, because they high higher risk to death.

5.2. Study Limitations

In Paper 1, main limitations are referred to the methodological quality among primary studies. The majority of them was not designed to evaluate the association TB-DM and/or used operational data from national TB programs. Also, DM status was not always defined with a prospective glucose test, leading to potential misclassification of DM status. Other methodological limitations were the lack of adjusting for confounding in most papers that were reviewed, and the population characteristics was mainly based in TB usual reported characteristics (age, gender, smear results) but not in DM factors (glucose level, BMI, waist circumference, lipids levels, blood pressure), so there is a high risk of unknown confounders not considered in primary study results. Finally, some studies had missing data, and was not addressed in the primary studies, increasing the risk of bias. However, the results keep the same direction than the previous review, with the advantage that this is focused in countries which struggle with weak health systems and with different epidemiology for TB and DM.

Our results in Paper 2 came from a prospective cohort, which took longer time that we expect and planned at the beginning, and the main reason for this delay was the lower prevalence of DM that was expected. We started with 3 clinics, and after one year when recruitment was slow (specially in TB-DM participants) we decide to include one more clinic, to speed up the recruitment. Regardless the TB-DM prevalence was lower than we expect, and lower than in the other TANDEM sites, the prevalence of 9.1% was higher than the prevalence found in general population in Peru(11). Another issue we faced during the recruitment were strikes from health workers at the primary care clinics where we recruit (one of the strikes takes more than 4 months). Our good relationship with the health workers permit us to enroll patients during these months, but because during the

strike doctors didn't attend all the patients who visit the TB clinic for diagnosis and treatment, our recruitment was slower during these months.

Although the use of the National TB program MDR-TB dataset for Paper 3 was a rich source of information, as any operational dataset, had some limitations: missing data (identified as missing at random) was frequent in a key variable (BMI), chest X-Ray results and (in much lower frequency) HIV status. Also, DM status information was recorded as a binary variable, and more info (date of diagnosis, comorbidities, DM complications, HbA1c) were not available, reason why was not possible to have a better characterization of this population. Nevertheless, this study was done in close collaboration with the Peruvian National TB program, providing access to clinical records in the cases who had missing data, reducing the amount of final missing data and provide an almost 2000 MDR-TB patients cohort. Further analysis with the new cohort of patients are planned with the National TB program, with the lessons learned in this study to catch as much information as possible.

5.3. Recommendations for future research

Our results provide more evidence for a better understanding of TB-DM in Peru and in similar settings; however, there are still many questions to solve to address this problem. Future research should cover the following areas:

- *Epidemiological studies:* Although there are some studies exploring TB-DM in Peru before our work (13-16), there is still a lack of epidemiological information for a better understanding of TB-DM problem in a Peruvian context, in part by the lack of primary designed TB-DM studies (all TB-DM previous studies in Peru before our work are a secondary analysis and/or based on clinical records, which is prone for bias and confounding), but also because DM epidemiological information is still not complete: just only in recent years started to appear better-designed studies in DM and other NCDs in Peru(17-21) for a better comprehension of DM situation in Peru. Nowadays there is a great opportunity to fill these information gaps because the Peruvian TB program has, since 2015, a

new electronic database (SIGTB)(22) to register all clinic and demographic information among all TB patients in Peru, making SIGTB a great and helpful tool to fill gaps on the TB-DM epidemiological background knowledge in Peru. This electronic database is linked with a unique identifier for TB patients, so in next years will be possible to evaluate the risk of relapse and the epidemiological pattern in Peruvian TB-DM population (such as *M. tuberculosis* resistant pattern in this population for example). Also, considering TB-DM population is older compared with general TB population, epidemiological characteristics and risk factors for TB should be evaluated in people over 35 years old to identify potential risk factors, with the aim to implement prevention activities tailored to this population. The evidence that could arise from these studies will help to bring more information with higher quality about TB-DM in LMICs, because still many of the studies on TB-DM were made in high income countries, with different level of health systems and with a lower TB prevalence, thus making it a completely different scenario for TB-DM compared with LMICs' settings.

- *Operational research:* Many problems around TB-DM (and in TB in general) are based in the complexity and needs of health systems at LMICs like Peru. We just started in mid-2016 a study in collaboration with the Peruvian TB Program to identify the gaps and barriers in health system that affect TB-DM patients. This study's ("cascade of care of TB-DM") approach was used before in HIV(23-26) and there are examples in DM(27, 28) and TB(29) too. We realized during the prospective study (Paper 2), the many weaknesses in the Peruvian health system to provide basic support in DM management and care, despite it is fully covered (diagnosis, treatment and medical care for free for TB patients) by the National Insurance Program (called Seguro Integral de Salud – SIS in spanish)(30). One of the most frequent barriers that we identify in the interaction with the participants in the prospective study was the lack of endocrinologist or a DM trained health worker at the primary health care, making very difficult the DM care for TB population, because, under Peruvian DM guidelines, any patient with DM who is diagnosed with TB should be evaluated and clinical managed by an

endocrinologist. Another important barrier we identify was the lack of tests for DM (fasting glucose and HbA1c): HbA1c is still very difficult to access in the biggest national hospitals in the country, since there is a shortage of reagents. We expect that the lessons learned as a result of this operational research would help with better evidence for TB-DM care in settings similar to Peru, where TB prevalence is still high and DM prevalence is increasing.

- *Better reporting and data quality:* The big problem that arises in our systematic review (and in the previous one, published in 2011(8)) was the low methodological quality of TB-DM research, leading us to deal with several issues on bias and unmeasured confounders (and in some cases, with the role of chance, because the studies were underpowered). Despite the evidence of the association between TB-DM with poor TB treatment outcomes is relatively strong, due to the complexity of DM clinical presentation, future studies should consider not only the classic confounders used in TB research (age, gender, socio-economic status, BMI, level of education) but also confounders such as HbA1c (or other glucose tests as fasting blood glucose or OTTG), time with DM diagnosis, DM comorbidities, blood pressure, lipids levels and DM treatment to characterize better this population and with the aim to reduce the role of confounding when the association between DM and TB treatment outcomes is evaluated. Unfortunately, this is very common in TB research(31), because many studies uses operational data from TB national programs (as in our Paper 3), observing problems such as missing data, representativeness and lack of important confounders for example.

5.4 Policy Implications

Our results highlight the strong association between two important diseases (TB and DM) in Peru, and, despite the limitations in these studies, this dissertation's results have policy implications for the control of TB-DM in an urban area in Peru (and potentially can be extrapolate to similar settings). An effective control among TB-DM would reduce the impact of DM in TB patients in Peru, a setting with several issues threatening TB control,

like a high prevalence of drug resistance (with the higher number of MDR-TB in the Americas)(1) and a scenario with a projected increasing of DM prevalence in the next 10 years(32). Our findings in our systematic review (Paper 1) supports previous evidence regarding the special attention that should be focused in TB treatment outcomes among TB-DM patients, which seems to have a stronger association with poor TB treatment outcomes in countries with high burden for both diseases. In Peru, there are several issues regarding adherence and treatment intermittency (factors directly associated with treatment outcomes), which, unfortunately was not possible to address in the systematic review (due the lack of reporting of these factors by primary studies), but should be observed in detail during treatment monitoring of TB-DM patients, based on the evidence of higher risk for poor TB treatment outcomes.

Our results in Paper 2 showed the high prevalence of DM among TB patients over 35 and with a BMI> 25 kg/m^2, showed the urgent necessity to tailored the TB program (including DOT) for this population, with implementation of DM nutrition counselling and universal glucose testing (HbA1c if there are resources available, if is not at least with 2 times fasting blood glucose) among this population. Right now, the glucose testing at TB diagnosis is around 60% in Peruvian TB patients and is done using fasting blood glucose (Personal communication: Peruvian National TB program), leaving almost 40% of TB patients in Peru without known their DM status. The lack of glucose test is mainly explained on the logistic capacity of the primary care center, where very often there is a lack of reagents. Also, during our prospectively work on Paper 2, we observed through our interaction and interviews with the participants and TB health workers, the urgent need to stablish a good channel for interaction between TB program and DM programs, because in settings like Peru, where NCDs control programs usually are neglected, the interaction for referral between services is very complicated, but should be addressed(33-36). Previous experiences in TB-HIV program integration maybe can provide some evidence and hints to how integrate TB and DM programs(37, 38).

In our Paper 3, we explore the role of DM among MDR-TB population in Lima, showing an increased risk for death among this population. Our findings demonstrate the

necessity among these patients to have a close glucose monitoring and DM care, including further evaluation on DM complications to reduce the risk of death. Although the mortality described in our Paper 3 didn't stablish if the cause of death was TB or not, evidence showed DM mortality in settings like Peru is caused by many reasons such as stroke, renal failure and infections(2), and these patients should be evaluated also in their blood pressure, renal function and lipids levels, with a comprehensive DM and cardiovascular evaluation to reduce mortality risk. Age should be considering also an important factor for MDR-TB patients with DM: our findings showed an older population compared with MDR-TB without DM, and tailored TB programs (as is suggested above) should be done for this population.

Finally, an important policy implication as a result of our findings is the higher frequency of comorbidity TB-DM than TB-HIV in these populations: in Paper 2 TB-DM was 9.1% and in TB-HIV was 1.9%; in Paper 3 HIV in MDR-TB population is around 4%, however DM prevalence (as we stated in the limitations in Paper 3, can be this prevalence underestimated) is higher (6.4% in whole study population, with almost 20% DM prevalence among patients over 35 years old). As we noted above, TB-DM program integration (observing previous experiences in TB-HIV services) should be addressed to achieve an adequate control of TB-DM problem.

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15.   Carrion-Torres O, Cazorla-Saravia P, Torres Sales JW, Yhuri Carreazo N, De La Cruz Armijo FE. Characteristics of the diagnosis and treatment of pulmonary tuberculosis in patients with and without diabetes mellitus type 2. Revista peruana de medicina experimental y salud publica. 2015;32(4):680-6.

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21.   Miranda JJ, Bernabe-Ortiz A, Diez-Canseco F, Malaga G, Cardenas MK, Carrillo-Larco RM, et al. Towards sustainable partnerships in global health: the case of the CRONICAS Centre of Excellence in Chronic Diseases in Peru. Globalization and health. 2016;12(1):29.

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28.   Vedanthan R, Kamano JH, Bloomfield GS, Manji I, Pastakia S, Kimaiyo SN. Engaging the Entire Care Cascade in Western Kenya: A Model to Achieve the Cardiovascular Disease Secondary Prevention Roadmap Goals. Global heart. 2015;10(4):313-7.

29.   Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. The Lancet Infectious diseases. 2016.

30.   Alcalde-Rabanal JE, Lazo-González O, Nigenda G. Sistema de salud de Perú. salud pública de méxico. 2011;53:s243-s54.

31.   Schumacher SG, Sohn H, Qin ZZ, Gore G, Davis JL, Denkinger CM, et al. Impact of Molecular Diagnostics for Tuberculosis on Patient-Important Outcomes: A Systematic Review of Study Methodologies. PloS one. 2016;11(3):e0151073.

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34.   Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. The Lancet Diabetes & Endocrinology. 2014;2(9):740-53.

35.   WHO. Collaborative Framework for Care and Control of Tuberculosis and Diabetes. Geneva2011.

36.   Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. The Lancet infectious diseases. 2009;9(12):737-46.

37.   Harries AD, Kumar AM, Satyanarayana S, Lin Y, Zachariah R, Lonnroth K, et al. Addressing diabetes mellitus as part of the strategy for ending TB. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2016;110(3):173-9.

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6. <u>Curriculum Vitae</u>

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Universidad Peruana Cayetano Heredia (Peru)	MD	2005	Medicine
London School of Hygiene and Tropical Medicine (UK)	MSc	2009	Epidemiology
Johns Hopkins Bloomberg School of Public Health (US)	PhD	2016	Global Diseases Epidemiology and Control

Positions and Honors.

Positions and Employment

5. Feb 2001:   Organizer of the First Latin America Permanent Workshop of Human Rights and Health.
6. Feb 2003 – Dec 2004:   Internship. Hospital Nacional Cayetano Heredia – Lima, Peru
7. Aug 2004 – Nov 2005:   Local Coordinator of the First Latin America and Caribbean Meeting of Young Leaders about Youth, HIV/AIDS and Human Rights. Sponsors: UNESCO and UNAIDS
8. Apr 2005 – Jun 2005:   Collaborator of the UNFPA Report "GYP Reporting on Progress Made Towards UNGASS Targets"
9. Apr 2005 – Jul 2008:   Research Assistant. Instituto de Medicina Tropical Alexander Von Humboldt (IMTAvH). Universidad Peruana Cayetano Heredia (UPCH).
10. Jan 2007 – Dec 2008:   Regional Focal Point Officer of IFHHRO (International Federation of Health and Human Rights Organizations)
11. Dec 2007:   Coordinator of IFHHRO Course of Human Rights and Health. Lima, Peru.

12. Nov 2007 – Jul 2008:   Coordinator of Project "Implementation of Rapid Test for MDR-TB (MODS) in public sector"
13. Aug 2008 – Present: Research Associate. Tuberculosis Research Unit. IMTAvH. UPCH
14. Oct 2008 – Present: Visiting Researcher. Imperial College London (UK)
15. Oct 2009 – Present: Tutor. MSc Clinical Trials. London School of Hygiene and Tropical Medicine (LSHTM)
16. Jan 2012 – Feb 2013:   Teaching Assistant. Department of International Health (Bloomberg Johns Hopkins School of Public Health - JHSPH)
17. Jun 2012 – Present: Research Assistant. Department of Epidemiology (JHSPH).
18. Mar 2012 – Jul 2013:   Teaching Assistant. Department of Epidemiology (JHSPH)
19. Apr 2014 - Present: Lecturer. Epidemiology Courses. Master of Epidemiology Research. UPCH
20. Sep 2015 - Present: Member. Institutional Review Board. UPCH
21. Dec 2015- Present: Honorary Lecturer. LSHTM
22. Aug 2016 – Present: Clinical Instructor. School of Medicine. UPCH

Professional Memberships

- 2005 – pres: Peruvian College of Physicians. N° 46148
- 2011 – pres: The UNION International Union Against Tuberculosis and Lund Disease. N° CU-0643273

Other Experiences

- August 2003:   Clinical Rotation. Instituto Emilio Ribas, Sao Paulo (Brazil)
- Oct 2009 – Present: Statistical Reviewer. The Lancet.
- Aug 2010 – Present: Invited Reviewer. Epidemiology & Infection
- Jun 2010 - Dec 2011:   Member. Research Committee. Peruvian College of Physicians
- Dec 2014 – Present: Associate Editor. BMC Research Notes

Other training

- 2005:   Course: "Monitoring the Right to Health", at the International Human Rights Academy, Cape Town (S. Africa)
- 2008:   10th Annual Ethical Issues in International Health Research Workshop, at Harvard School of Public Health.
- 2010:   Annual International Public Health Summer Institute, University of Alabama at Birmingham.

Ethics Certificate

- 2015: JHSPH Basic Human Subjects Research Course (Expiration Date 23 May 2020)

Selected peer-reviewed publications

1. Gianella C, **Ugarte-Gil C**, Lema C, Caro G, Aylas R, Castro C. Tuberculosis in vulnerable populations: the case of an indigenous community in the Peruvian Amazon. Health and Human Rights Journal 2016; 18(1): 55-68
2. Altez-Fernandez C, Seas C, Zegarra L, **Ugarte-Gil C**. Diseases masking and delaying the diagnosis of urogenital tuberculosis. Ther Adv Urol. 2016;8(3):234.
3. Sanchez Clemente N, **Ugarte-Gil C**, Solorzano N, Maguiña C, Moore D. An Outbreak of Bartonella bacilliformis in an Endemic Andean Community. PLoS One. 2016 Mar 18;11(3):e0150525
4. Kirwan DE, **Ugarte-Gil C**, Gilman RH, Caviedes L, Rizvi H, Ticona E, Chavez G, Cabrera JL, Matos ED, Evans CA, Moore DA, Friedland JS. Microscopic Observation Drug Susceptibility Assay for Rapid Diagnosis of Lymph Node Tuberculosis and Detection of Drug Resistance. J Clin Microbiol. 2016; 54(1):185-9.
5. Saldanha IJ, Li T, Yang C, **Ugarte-Gil C**, Rutherford GW, Dickersin K. Social network analysis identified central outcomes for core outcome sets using systematic reviews of HIV/AIDS. J Clin Epidemiol. 2016; 70:164-75.
6. Lambert AA, Lam JO, Paik JJ, **Ugarte-Gil C**, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One. 2015; 10(6):e0128004
7. Ong CW, Elkington PT, Brilha S, **Ugarte-Gil C**, Tome-Esteban MT, Tezera LB, Pabisiak PJ, Moores RC, Sathyamoorthy T, Patel V, Gilman RH, Porter JC, Friedland JS. Neutrophil-Derived MMP-8 Drives AMPK-Dependent Matrix Destruction in Human Pulmonary Tuberculosis. PLoS Pathog. 2015;11(5):e1004917
8. Scherer RW, **Ugarte-Gil C**, Schmucker C, Meerpohl JJ. Author's reasons for unpublished research presented at biomedical conferences: a systematic review. J Clin Epidemiol. 2015;68(7):803-10.
9. Millard J, **Ugarte-Gil C**, Moore DAJ. Multidrug resistant tuberculosis. BMJ. 2015;350:h882.
10. **Ugarte-Gil C**, Elkington PT, Gotuzzo E, Friedland JS, Moore DA. Induced Sputum is Safe and Well-Tolerated for TB Diagnosis in a Resource-Poor Primary Healthcare Setting. Am J Trop Med Hyg. 2015;92(3):633-5
11. Valenzuela C, **Ugarte-Gil C**, Paz J, Echevarria J, Gotuzzo E, Vermund SH, Kipp AM. HIV Stigma as a Barrier to Retention in HIV Care at a General Hospital in Lima, Peru: A Case-Control Study. AIDS Behav. 2015;19(2):235-45.
12. Riza AL, Pearson F, **Ugarte-Gil C**, Alisjahbana B, van de Vijver S, Panduru NM, Hill PC, Ruslami R, Moore D, Aarnoutse R, Critchley JA, van Crevel R. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol. 2014;2(9):740-53

13. **Ugarte-Gil C**, Moore DA. Tuberculosis and diabetes co-morbidity: an unresolved problem. Rev Peru Med Exp Salud Publica. 2014;31(1):137-42
14. **Ugarte-Gil C**, Ponce M, Zamudio C, Canaza L, Samalvides F, Seas C. Knowledge about HIV prevention and transmission among recently diagnosed tuberculosis patients: a cross sectional study. BMC public health. 2013;13(1):1237.
15. **Ugarte-Gil C**, Ruiz P, Zamudio C, Canaza L, Otero L, Kruger H, et al. Association of major depressive episode with negative outcomes of tuberculosis treatment. PLoS One. 2013;8(7):e69514.
16. **Ugarte-Gil CA**, Elkington P, Gilman RH, Coronel J, Tezera LB, Bernabe-Ortiz A, et al. Induced Sputum MMP-1, -3 & -8 Concentrations during Treatment of Tuberculosis. PLoS One. 2013;8(4):e61333.
17. Loh LC, **Ugarte-Gil C**, Darko K. Private sector contributions and their effect on physician emigration in the developing world. Bull World Health Organ. 2013;91(3):227-33.
18. Llerena Luna C, Schweig Groisman M, **Ugarte-Gil CA**. Knowledge, attitudes, and practices about Carrion's disease in rural Ancash, Peru. Rev Panam Salud Publica. 2013;33(5):311-5.
19. Sanchez Clemente N, **Ugarte-Gil CA**, Solorzano N, Maguina C, Pachas P, Blazes D, et al. Bartonella bacilliformis: a systematic review of the literature to guide the research agenda for elimination. PLoS Negl Trop Dis. 2012;6(10):e1819.
20. Ponce M, **Ugarte-Gil C**, Zamudio C, Krapp F, Gotuzzo E, Seas C. Additional evidence to support the phasing-out of treatment category II regimen for pulmonary tuberculosis in Peru. Trans R Soc Trop Med Hyg. 2012;106(8):508-10.
21. Elkington PT, **Ugarte-Gil CA**, Friedland JS. Matrix metalloproteinases in tuberculosis. Eur Respir J. 2011;38(2):456-64.
22. Elkington P, Shiomi T, Breen R, Nuttall RK, **Ugarte-Gil CA**, Walker NF, et al. MMP-1 drives immunopathology in human tuberculosis and transgenic mice. J Clin Invest. 2011;121(5):1827-33.

Languages

- Spanish: Native speaker
- English: IELTS Band Score 7/9
- Portuguese: Reading

Research Support
Ongoing Research Support

WDF15-1224, World Diabetes Foundation   Ugarte (PI)   01/03/16-28/02/18
Linkage between Tuberculosis and Diabetes
The goal of this project is to provide evidence and training on TB-DM among health workers in Lima, Peru
Role: PI

MR/P004172/1, MRC (UK)   Moore (PI)   01/07/16-30/06/17
Examining health system performance for indigenous people in the Peruvian Amazon through the lens of tuberculosis control.
Role: Co-Investigator

Completed Research Support
Wellcome Trust Grant 085777/Z/08/Z   Ugarte (PI)   08/01/08-05/31/11
Master's Training Fellowship in Public Health - Research project: "MMPs and therapeutic response in tuberculosis".
Role: PI

ISID Small Grant   Ugarte (PI)   07/27/10–06/30/12
Detection and susceptibility testing for Tuberculosis in lymph node tissue using the MODS method
The goal of this project was to evaluate MODS method for TB diagnosis in lymph node tissue
Role: PI

1U2RTW007368-   01A1   Gotuzzo (PI)   05/20/10-02/28/12
ICOHRTA Peru Small Grant: Project Depression and Tuberculosis
The goal of this project was to evaluate the association of depression with Tuberculosis treatment outcomes
Role: SubAward – PI

R25 TW009340-02   Van der Horst (PI)   10/01/13-12/30/15
Fogarty Global Health Fellowship
This fellowship has the following project "Matrix Metalloproteinases (MMPs) and their degradation products correlation with Tuberculosis, TB/Diabetes Mellitus and TB/HIV" and the aim is to evaluate the role of MMPs in TB, TB/DM and TB/HIV
Role: Fellow

WHO/TDR Small Grant   Ugarte (PI)   05/30/15 -12/31/15
Diagnosis of Latent Tuberculosis among Diabetes ambulatory patients in Lima, Peru
This project aims to calculate the prevalence of Latent Tuberculosis among Diabetes ambulatory patients in an area of high prevalence of active Tuberculosis in Lima, Peru and identify risk factors for latent Tuberculosis.
Role: Principal Investigator