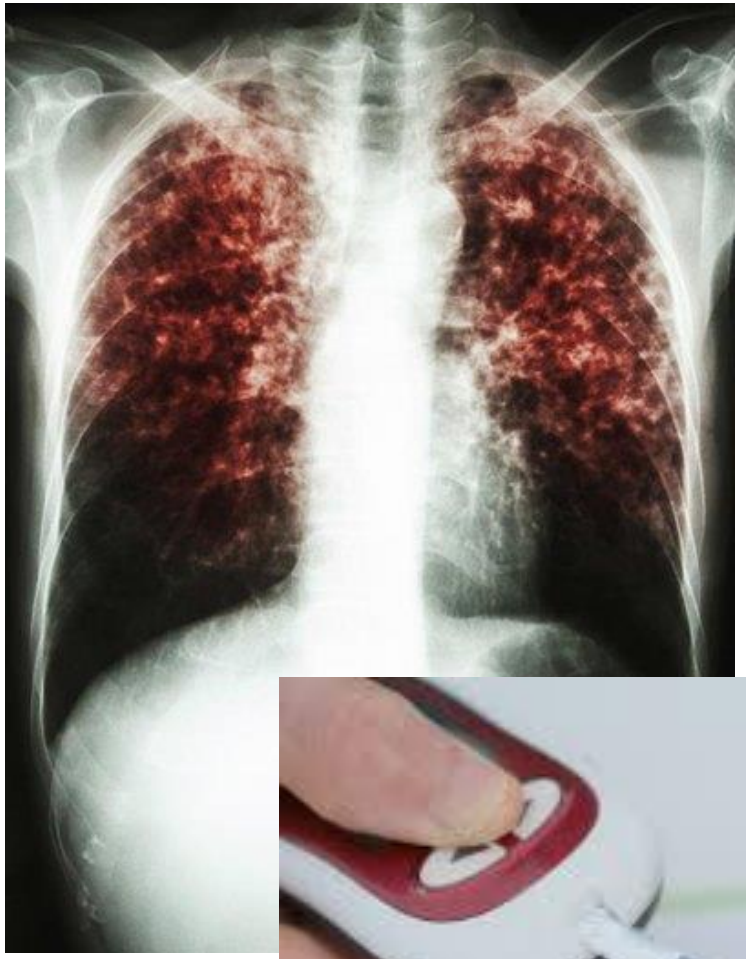

ZERO TB Initiative

A COMPREHENSIVE APPROACH FOR TB ELIMINATION

UNDERSTANDING THE SYNERGY BETWEEN TUBERCULOSIS AND DIABETES

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WHO EURO Virtual Medical Consilium on DR-TB

WHO EURO Regional Office
Copenhagen, Denmark (Via Zoom)
February 5, 2021

Plan for todays presentation

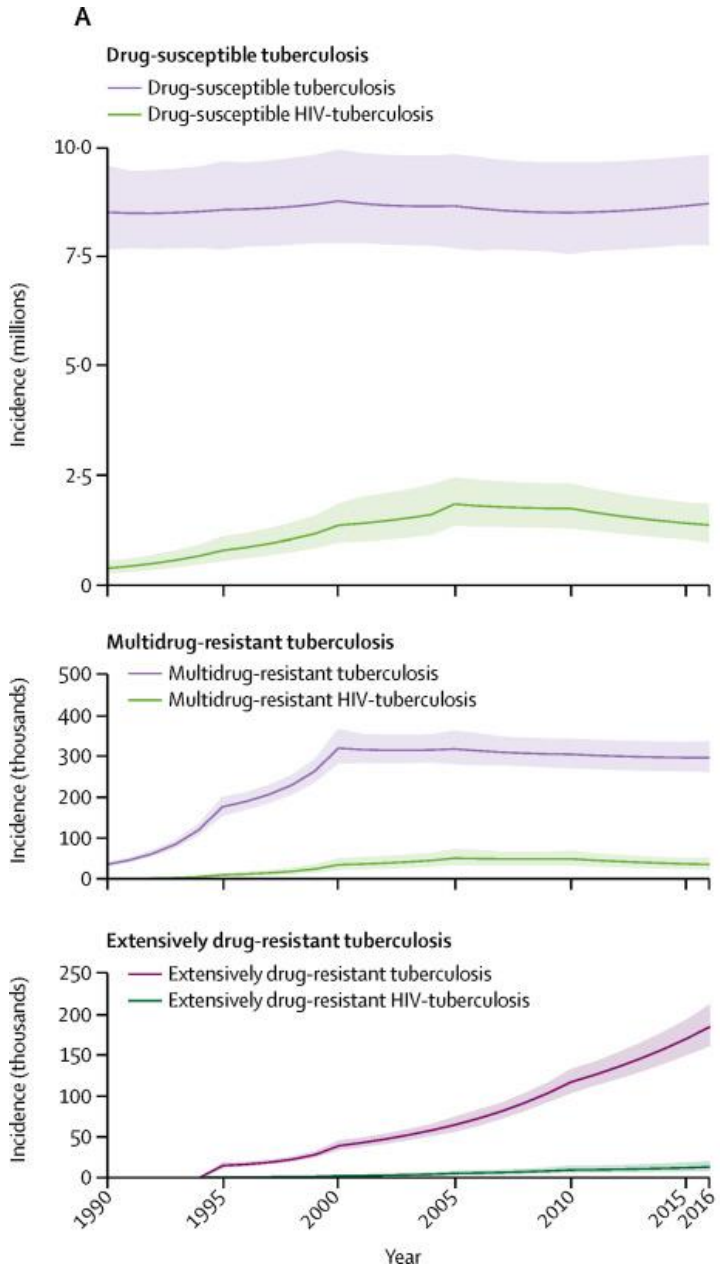
1. Global burden of TB and diabetes
2. Synergy between TB and diabetes
3. Mechanisms of pathogenesis
4. How should this knowledge affect practice?
   - Search
   - Treat
   - Prevent

We will not meet global TB goals with our current rates of decline

Drug-sensitive TB *declined* 1.3% per annum from 2006-2016 (age standardized)

MDR-TB *declined* 2.1%per annum from 2006-2016

XDR-TB *increased* 7.9% per annum from 2006-2016

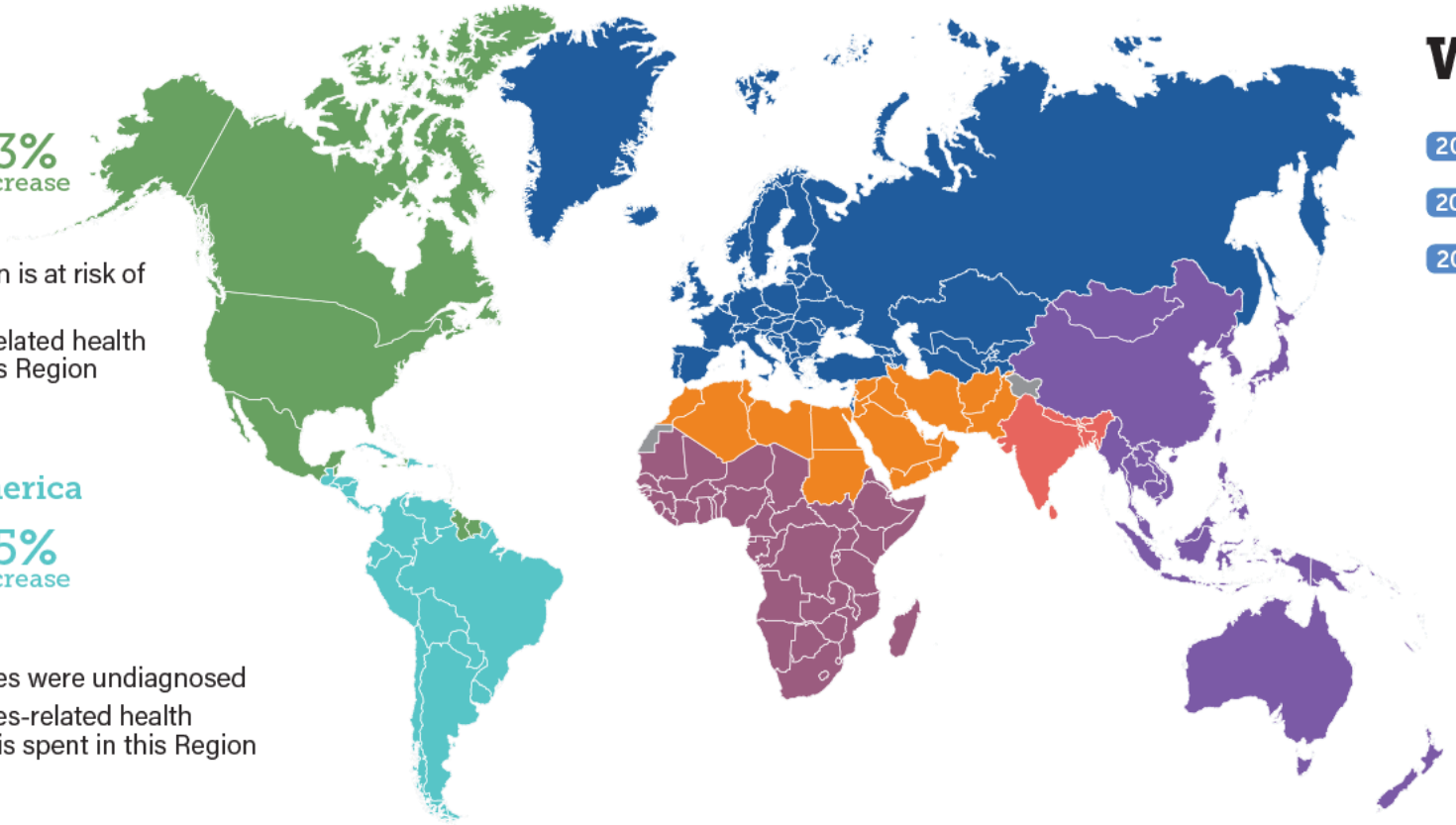


More than 4,000 people die from TB *every day*

Source: *Lancet ID*, 2018

Rising rates of diabetes are a concern for the TB-elimination agenda

Number of adults (20–79 years) with diabetes worldwide



North America & Caribbean

2045 63 million
2030 56 million
2019 48 million

↑ 33% increase

- 1 in 6 adults in this Region is at risk of type 2 diabetes
- 43% of global diabetes-related health expenditure occurs in this Region

South & Central America

2045 49 million
2030 40 million
2019 32 million

↑ 55% increase

- 2 in 5 people with diabetes were undiagnosed
- Only 9% of global diabetes-related health expenditure for diabetes is spent in this Region

WORLD

2045 700 million
2030 578 million
2019 463 million

↑ 51% increase

Europe

2045 68 million
2030 66 million
2019 59 million

↑ 15% increase

- 1 in 6 live births are affected by hyperglycaemia in pregnancy
- The Region has the highest number of children and adolescents (0–19 years) with type 1 diabetes – 297,000 in total

Africa

2045 47 million
2030 29 million
2019 19 million

↑ 143% increase

- 3 in 5 people with diabetes are undiagnosed
- 3 in 4 deaths due to diabetes were in people under the age of 60

Middle East & North Africa

2045 108 million
2030 76 million
2019 55 million

↑ 96% increase

- 1 in 8 people have diabetes
- 1 in 2 deaths due to diabetes were in people under the age of 60

South-East Asia

2045 153 million
2030 115 million
2019 88 million

↑ 74% increase

- 1 in 5 adults with diabetes lives in this Region
- 1 in 4 live births are affected by hyperglycaemia in pregnancy

Western Pacific

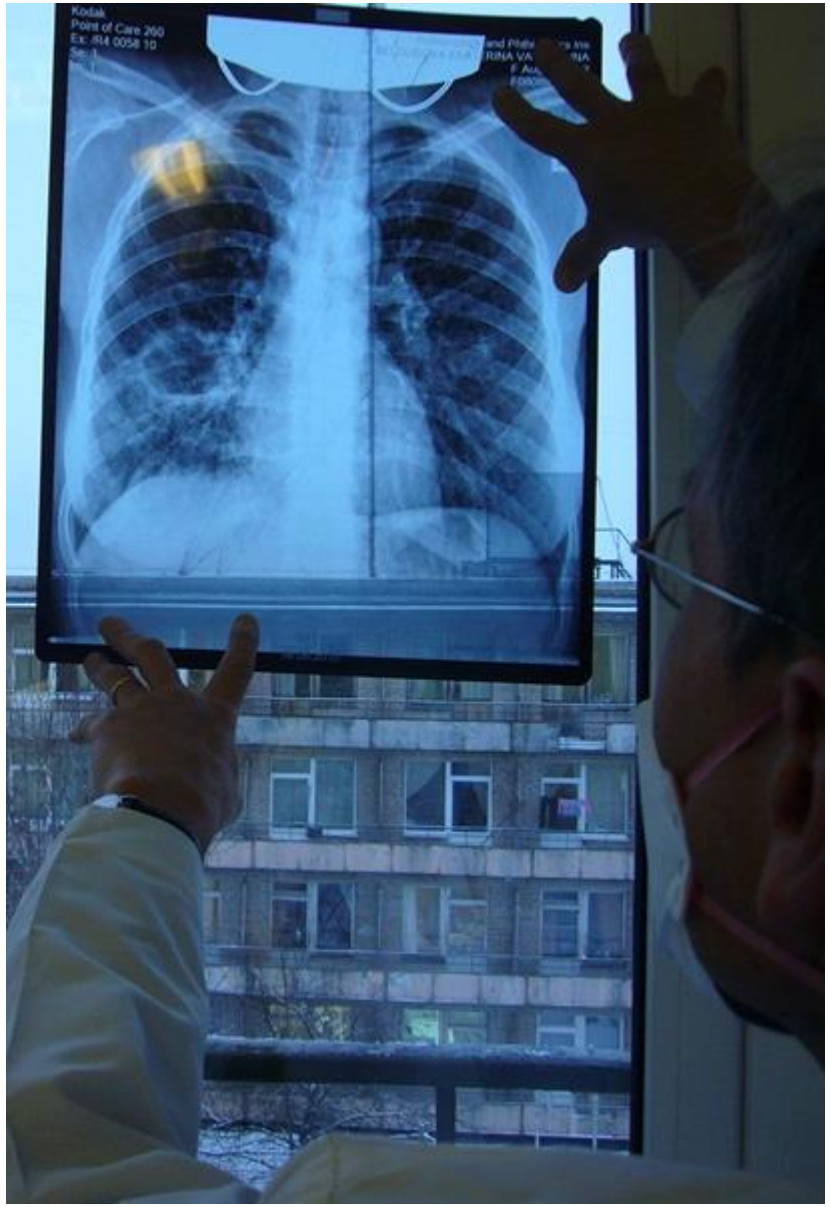
2045 212 million
2030 197 million
2019 163 million

↑ 31% increase

- 1 in 3 adults with diabetes lives in this Region
- 1 in 3 deaths due to diabetes occur in this Region

Source: International Diabetes Federation Atlas, 9th Edition, 2019

Synergy between TB and Diabetes



Scientific evidence

Jeon and Murray	2008	13 observational studies with 1,786,212 participants who had 17,698 TB cases	TB Disease RR = 3.11 (95% CI 2.27-4.26)	These findings provides the evidence base for suggesting that individuals with diabetes are three times as likely to develop TB than individuals without diabetes.
Lee et al.	2016	Aimed to look at the association between diabetes and TB infection. Included 13 studies comprised of 38,263 individuals (1 cohort study, 12 cross sectional studies).	TB infection RR = 4.40 (in singular cohort study; nonsignificant) and adjusted OR = 1.18 (in pooled cross sectional study analysis)	These findings suggest that the risk of TB infection is higher in diabetics.

Why does diabetes matter for TB elimination?

While there is significant geographic heterogeneity in the dual burden of TB and diabetes, a few systematic reviews have placed the prevalence of diabetes in individuals suffering from TB to be around 15% (Workneh et al. 2017; Noubiap et al. 2019).

One study by Pan et al. 2015 indicated that, in the 13 countries with the highest burden of TB, the rise in diabetes will contribute 6 million new cases and 1.1 million TB deaths over the next 20 years.

There is also some evidence to suggest that diabetes increases an individual's risk of developing not only drug-susceptible TB, but also DR-TB. This may be linked to challenges in treating people with TB-diabetes. A meta-analysis from 2018 by Tegegne et al. demonstrated that the risk of having MDR-TB among patients with both TB and diabetes may be 97% higher than in TB patients without diabetes.

TB-Diabetes in Europe

In a study of thirteen clinical centers located in 10 different European countries—the overall prevalence of diabetes among TB patients was **10.7%** (95% CI, 9.7%–11.9%)

In different countries, diabetes prevalence ranged from 4.4% in Greece to 28.5% in the United Kingdom.

Countries included: France (Briis-sous-Forges), Germany (Borstel), Greece (Thessaloniki), Italy (Rome and Genova), Norway (Oslo), Russia (Volgograd), Slovakia (Vysne Hagy), Spain (Barcelona, Madrid and Pontevedra), the United Kingdom (London), and Ukraine (Vinnytsia)

Source: Schepisi et al. 2019

SEARCH

SEARCH ACTIVELY · TEST PROPERLY

TREAT

TREAT EFFECTIVELY · SUPPORT THROUGH TREATMENT

PREVENT

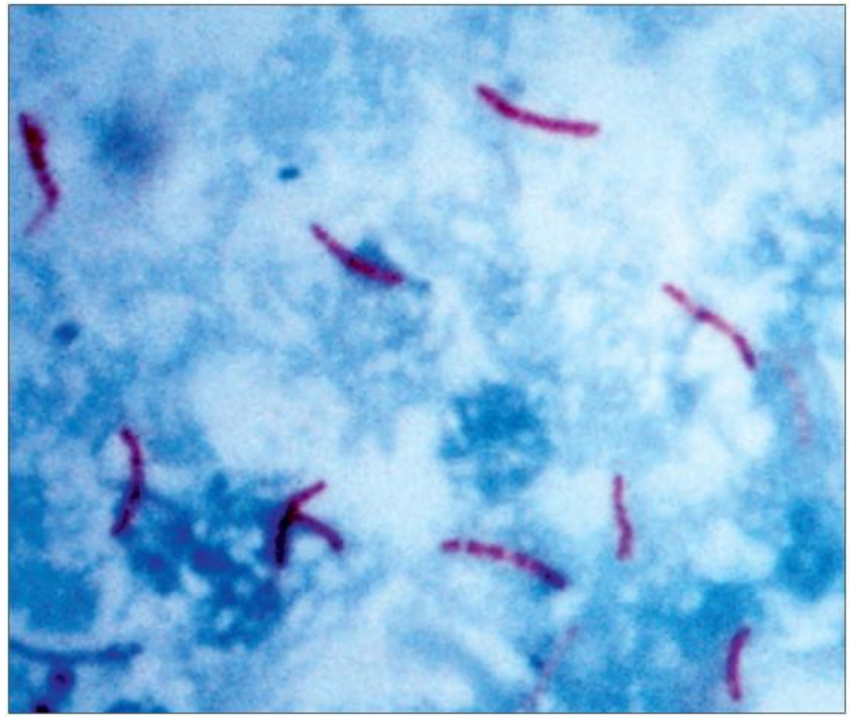
PREVENT EXPOSURE · TREAT EXPOSURE

CAN WE ELIMINATE TB IF WE DO EVERYTHING ELSE RIGHT BUT DO NOT ADDRESS DIABETES?

LIKELY NO.

WE HAVE TO ACCOUNT FOR DIABETES AS WE IMPLEMENT THE SEARCH-TREAT-PREVENT STRATEGY FOR TB ELIMINATION

Tuberculosis and Diabetes Mechanism of Pathogenesis



Diabetes and TB both affect the immune system

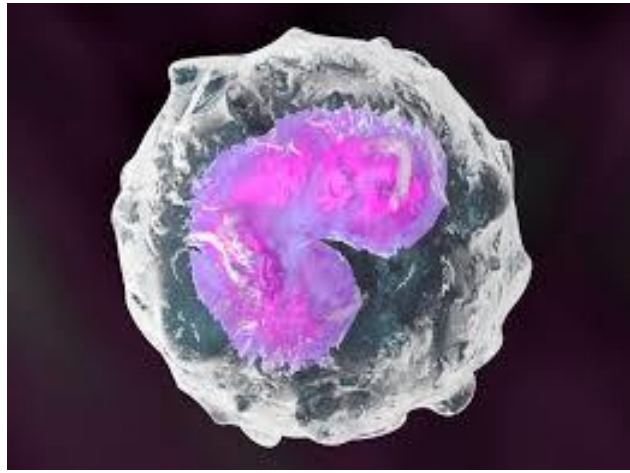
Diabetes is associated with **immune dysfunction** and alterations in the components of the immune system, including in levels of specific cytokines and chemokines.

This results in **decreased phagocytosis** of *M. tuberculosis* and **decreased expression of genes that help the body contain the bacterium**

Mycobacterium tuberculosis also causes immune dysfunction. It infects at least five distinct cell subsets in the lungs, including resident alveolar macrophages, neutrophils, monocytes, interstitial macrophages, and dendritic cells. It evades host immunity by:

- interfering with phagosome-lysosome fusion;
- resisting reactive metabolites of nitrogen and nitric oxide;
- interfering with antigen presentation by MHC class II molecules (and subsequent activation of T-cells)

Diabetes and Innate immunity: monocytes



Upon infection with *Mycobacterium tuberculosis*, they rapidly migrate to the lung, where they differentiate into macrophages and dendritic cells for antigen presentation and secretion of cytokines. Individuals with diabetes have less interaction between *M. tuberculosis* and monocytes at the lungs.

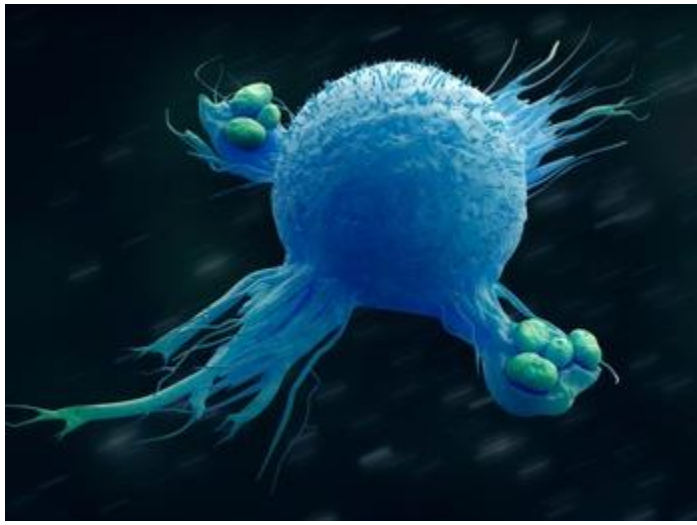
Why does this happen?

- Increased expression in diabetics of the monocyte protein CCR2 which affects the ability of the monocytes to migrate rapidly
- Reduced expression in diabetics of receptors like CD64 and CD206, which bind TB antigens. This makes the monocytes less effective

(Sources: Nethella and Babu 2017; Schlesinger et al. 1990; Stew et al. 2013; Martinez and Kornfeld 2014, 4; Dooley et al. 2009)

Diabetes and Innate immunity: macrophages

Even when monocytes differentiate into macrophages, there is evidence that in diabetics they are less “activated,” leaving the host more susceptible to TB infection.

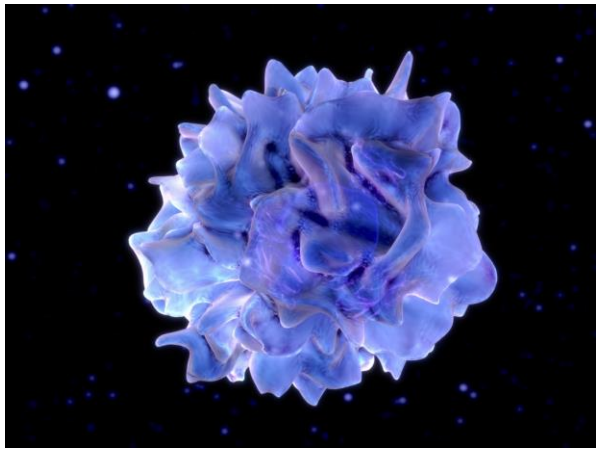


TB replicates within macrophages. These cells respond by creating a “respiratory burst” that results in the production of reactive oxygen species (ROS) that can kill mycobacteria.

Individuals who are hyperglycemic are known to have a less potent “respiratory burst”, which leaves them with fewer reactive oxygen species (ROS).

(Sources: Nethella and Babu 2017; Niazi and Kalra 2012)

Diabetes and Innate immunity: dendritic cells



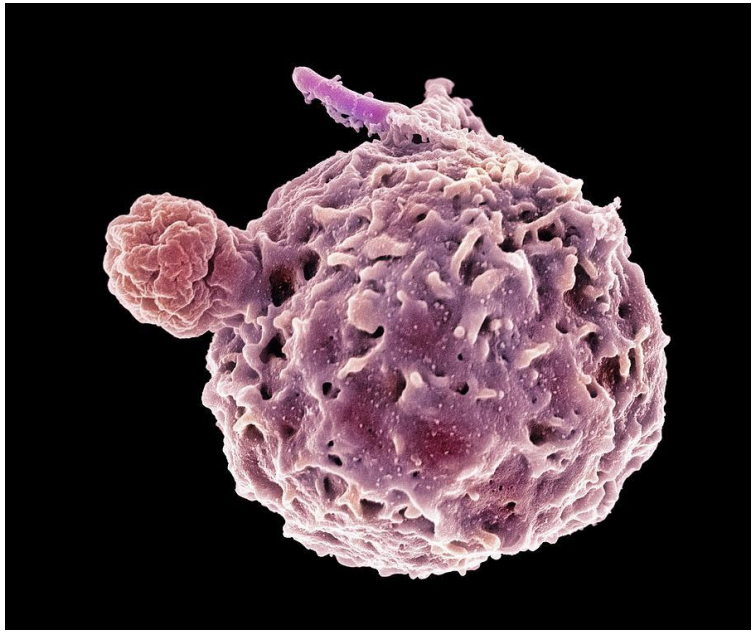
Dendritic cells (DC) are one of the crucial players in linking innate immune system to the adaptive immune system (T-cells and B-cells). They do this by capturing and processing mycobacterial antigens and presenting them to T-cells.

Studies in diabetics have reported reduced presence of dendritic cells at the site of TB infection, and reduced migration of dendritic cells to lymph nodes where they can activate T-cells.

(Source: Nethella and Babu 2017; Khader et al. 2006, Holt et al. 1987; Sertl et al. 1986; Kumar et al. 2016)

Diabetes and Innate immunity: Neutrophils

Neutrophils contribute to immune protection through oxidative killing of mycobacteria. They secrete cytokines (like IL-8, IL-1-β and IFN-γ), which signal and activate distant immune cell. They also create inflammation.

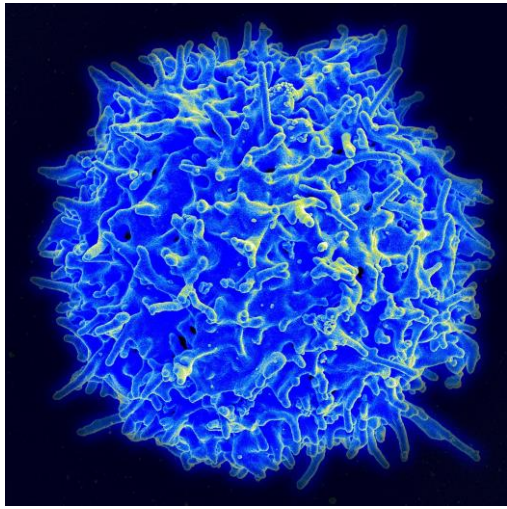


TB-Diabetes co-morbidity is characterized by heightened levels of absolute neutrophil counts. But… these neutrophils are impaired and have a decreased ability to phagocytose *M. tuberculosis.*

Sources: Nathella and Babu 2017; Anrade et al. 2014; Lowe et al. 2020;Berry et al. 2010; Raposo-Garcia et al. 2017; Mendoza-Aguilar et al. 2012; Hilda et al. 2019

Diabetes and Adaptive immunity: T-cells

Helper T-cells type I (Th-1) are important for initiating and maintaining a response against TB, but their numbers are reduced in individuals with diabetes.

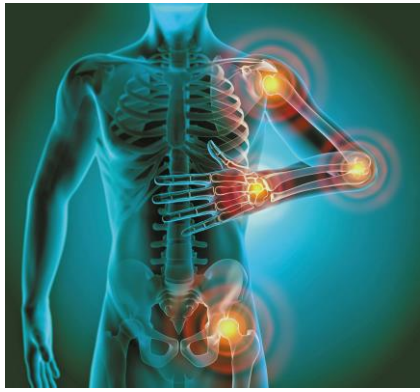


This leads to reduced cytokines: tumor necrosis factor (TNF-alpha and TNF-beta), interleukin-1, and interleukin-6 production.

The susceptibility of diabetes patients to TB is mainly due to reduced numbers and function of T-lymphocytes (the cytokines help inhibit Mycobacterium tuberculosis).

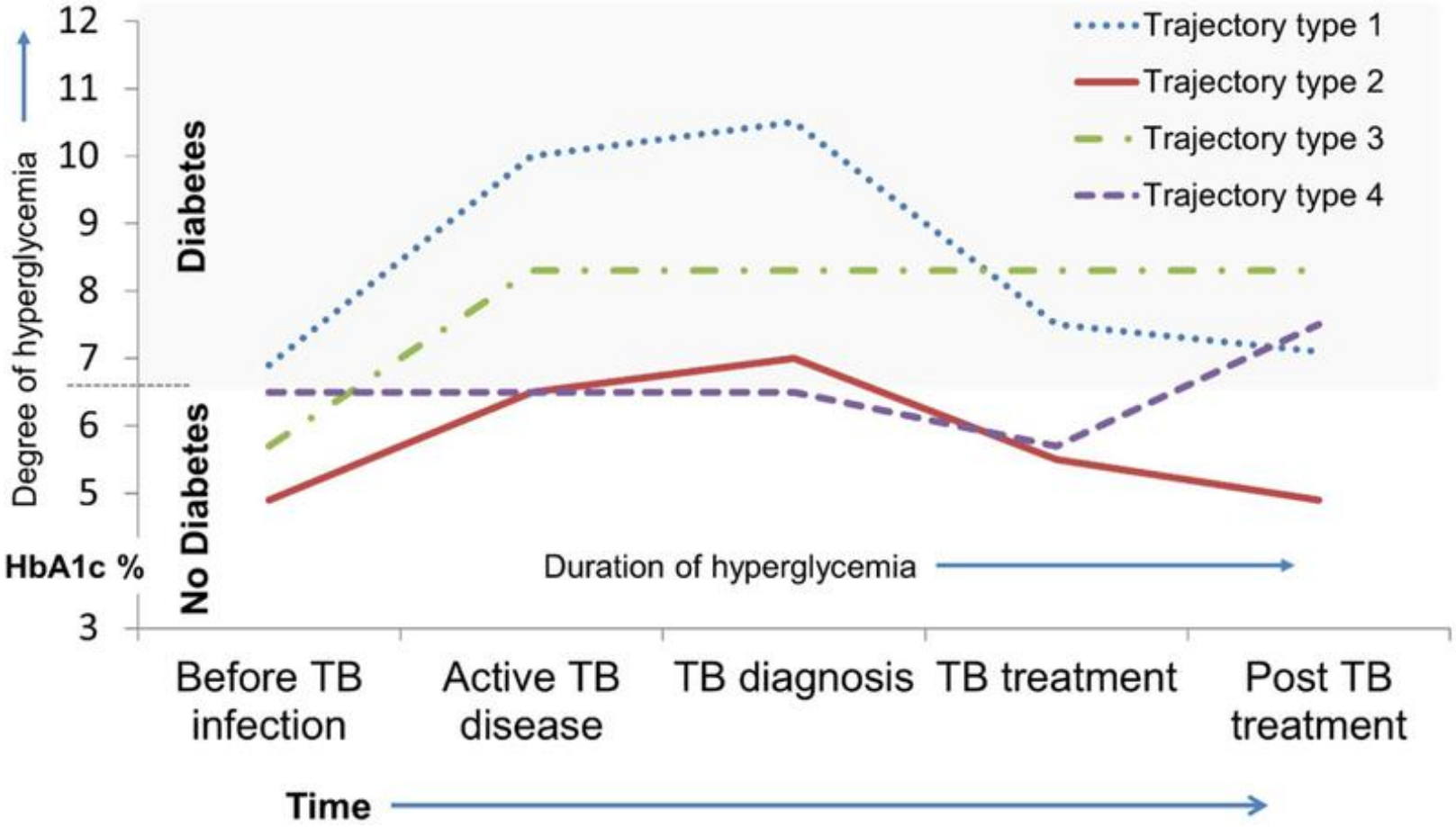
Sources: Niazi and Kalra 2012; Nathella and Babu 2018; Kumar et al. 2013; Yorke et al. 2017

Diabetes and Inflammation



- In diabetics there is a “hyper-inflammatory response”
- The amount of inflammatory cytokines in the plasma (pro-inflammatory) have a positive correlation with hemoglobin A1C levels.
- This suggests that impaired glucose control is associated with inflammation (regardless of sex, age, or other metabolic parameters).
- The stress response to infection by *M. tuberculosis* may also play a role in dysglycemia, mediated by pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-alpha.
- If a patient was hyperglycemic prior to developing active TB, the stress response may lead to exacerbated hyperglycemia or overt diabetes

Sources: Niazi and Kalra 2012; Nathella and Babu 2018; Kumar et al. 2013; Yorke et al. 2017



Hypothetical trajectories of blood glucose levels over the natural history of TB Among patients that experience TB-induced transient hyperglycemia, it is unknown what factors facilitate reversion to pre-TB blood glucose levels after TB treatment completion (Trajectory type 2) and what factors increase the likelihood of remaining elevated (Trajectory type 3) or later developing incident diabetes (Trajectory type 4).

From: Aftab H, Christensen DL, Ambreen A, et al. Tuberculosis-Related Diabetes: Is It Reversible after Complete Treatment? Am J Trop Med Hyg 2017;97:1099–102.

How does this affect practice?

Searching for **TB Disease** in people with diabetes

- People with TB should be screened for diabetes and vice versa
- Some studies suggest that atypical X-rays are seen more often in TB-DM patients. Often, diabetics have more lower lung field involvement (Skowronski et al. 2013), and they may be more likely to have cavitary lesions (Schepisi et al. 2019)
- The WHO (2016) recommends “overreading” of chest x-rays in individuals who are at-risk for producing any abnormal chest radiography, and proceed to bacteriological testing.
- Diabetics do not seem to differ in bacterial positivity and also have similar rates of extrapulmonary disease as non-diabetics (Schepisi et al. 2019)
- Symptoms: not clear if diabetics have worse symptoms or not. They may be more likely to have a persistent cough (with cavitary lesions on chest x-ray).

Sources: WHO 2011; WHO 2016; Skowronski et al. 2013; Schepisi et al. 2019; Riza et al. 2014; Paralija and Mujakovic 2018

Searching for **TB Infection** in people with diabetes

- While Jeon and Murray 2008 showed an increased risk for progression to active TB in individuals with diabetes, Harries et al. 2020 points out that the WHO does not currently recommend systematic screening for TB infection in individuals with diabetes.
- The current recommendation is to screen on an individual basis and treating infection if the initial test comes back positive. This may change with new evidence.
- In general, there is no difference between TST/IGRA in diabetics and non-diabetics, although some studies suggest that the IGRA test may give more false negatives in diabetics who are sputum smear negative

Sources: WHO 2016; Harries et al. 2020; Jeon and Murray 2008; Salindri et al. 2019; Walsh et al. 2011; Choi et al. 2015; Gan et al. 2014; Yamusue et al. 2020.

Treating **TB disease** in people with diabetes

In the *Collaborative Framework for Care and Control of Tuberculosis and Diabetes (2011)*, the WHO recommends that *"**Treatment and case management of TB in people with diabetes should be provided in accordance with existing TB treatment guidelines and international standards**. The same TB treatment regimen should be prescribed to people with diabetes as for people without diabetes"*.

In the case of DR-TB, the *WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment (2020)* and previous guidelines cautions against the use of nephrotoxic injectable agents in people with renal failure, with diabetics being a high risk group for this. It also states that although little data exists on the use of all oral shorter bedaquiline-containing regimens for people with diabetes, it remains as one of the treatment options.

There is also some concern about use of neurotoxic agents like linezolid in a population of people already prone to neuropathy.

But… there is some debate about whether treatment should be changed because of the dismal outcomes faced by people with TB and diabetes

Baker et al.	2011	33 studies investigating 7 different outcomes.	Failure and Death (combined) RR = 1.69 Death RR = 1.89 (unadjusted studies), 4.95 (in studies that adjusted for age and other sources of confounding). Relapse RR = 3.89 Recurrence: no statistically significant risk	
Huangfu et al.	2019	105 studies comprised of 56,122 individuals with TB-DM and 243,035 individuals with TB.	Death OR = 1.88 Relapse OR = 1.64 Culture conversion OR = 2.06 **Limited evidence suggests that TB-DM patients were twice as likely to develop MDR-TB OR = 1.98, which increased to OR = 2.22 for studies reporting adjusted estimates.**	

But… there is some debate about whether treatment should be changed because of the dismal outcomes faced by people with TB and diabetes

Perez-Navarro et al.	2017	507 people in Mexico, 183 (36%) of which had T2DM.	Treatment failure HR = 2.04 Relapse HR = 1.86 **When stratified by T2DM and smear-positivity at 2 months, there was an association with DR-TB OR = 6.68 and treatment failure OR = 4.7** This cohort was followed over seven years from the time of TB treatment until the end of the study.
Tegegne et al.	208	24 observational studies from 15 countries	**(Diabetes has significant association with MDR-TB; OR=1.97 (CI = 1.58 to 2.45)** **Went up to OR=2.43 (CI = 1.90 to 3.12)when adjusted for confounding** Association regardless of country income level, type of DM

But… there is some debate about whether treatment should be changed because of the dismal outcomes faced by people with TB and diabetes

Sahakyan, Varduhi and Abrahamyan	2019	621 individuals in Armenia, 5.8% of whom had DM	Treatment failure OR = 8.99 (after adjusting for weight and sputum smear status) Other outcomes like death and loss to follow-up were not found to be significant between the two groups.	
Dooley et al.	2009	297 people in Baltimore, USA, of which 42 (14%) had DM	Death OR = 2.0 (adjusted OR increased to 6.5) Culture conversion p = 0.09, did not achieve significance, but was longer in the DM group compared to the non-DM group They felt that this would have implications for the duration of treatment and possible relapse.	

But… there is some debate about whether treatment should be changed because of the dismal outcomes faced by people with TB and diabetes

- The **increased time to culture conversion** may explain the higher rates of relapse among TB-DM patients, and also it may contribute to the risk of the development of drug resistance.
- **Some argue that treatment of TB in people with diabetes should differ** because of the increased risk of developing drug-resistance, time to culture conversion, toxicity, treatment failure, recurrence, and decreased bioavailability of certain anti-tubercular drugs in individuals with large body mass (associated with diabetes)
- This may include increasing the length of treatment, using higher doses of anti-tubercular medicines, **earlier tailoring of regimen with DST**, and the use of immunomodulators.

Sources: van Crevel et al. 2018; Riza et al. 2014; Dooley et al. 2008)

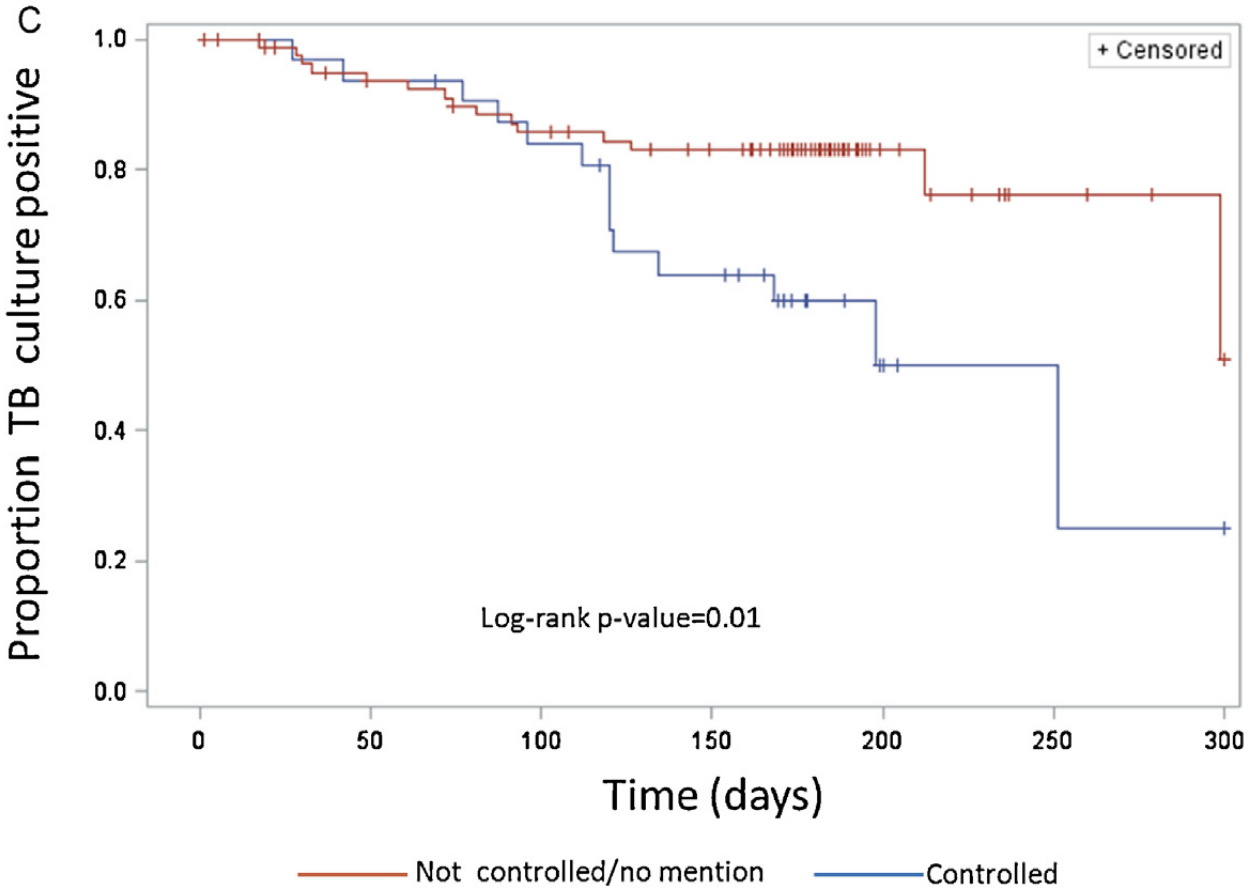
Treating **TB disease** in people with diabetes

People do agree on the need to maintain glycemic control

- since hyperglycemic states seem to limit an effective immune response on TB, it's vital that glycemic levels remain stable throughout the course of treatment (Goal of HbA1c of < 7.0%; difficult to achieve)
- We also know that having uncontrolled blood glucose and abnormally high HbA1c levels are associated with not only the development of active TB, but also many of the poor outcomes discussed.

Sources: Viney, Mills and Harley 2019; Magee et al. 2013; Esmail et al. 2018

Magee et al.	2013	1671 people in Peru, of which 186 (11.1%) had DM	Culture conversion HR = 2.5 (for controlled versus uncontrolled DM) and HR = 2.1 (for individuals who sought frequent DM care during TB treatment) TB-DM patients were more likely to be culture positive at the time of diagnosis



Kaplan–Meier curves for time until TB culture conversion from positive to negative by diabetes control status among patients with diabetes mellitus who have not been previously treated for TB (n = 117).

Treating **TB disease** in people with diabetes

People do agree on the need to maintain *glycemic control*

- Of drugs that exist to control blood glucose, the use of **metformin** has been shown to significantly decreases risk of death in individuals with tuberculosis. It does have drawbacks, which will be discussed by my colleague.
- Sulphonylurea drugs and insulin are two other useful options.

Sources: Viney, Mills and Harley 2019; Magee et al. 2013; Esmail et al. 2018

Metformin

Zhang and He	2019	18 studies (16 cohort studies, 1 case control, and 1 cross sectional study) comparing the effect of metformin on TB in individuals with DM	Prevalence of TB Infection RR = 0.61 (although the evidence for this statistic is less certain) TB Incidence RR = 0.51 Death RR = 0.34 Recurrence RR = 0.55 (although this did not achieve significance).	MET may inhibit growth of Mtb via an AMPK-dependent pathway and ameliorate lung pathology Enhances autophagy; increase the production of mitochondrial reactive O_2 species, decreases inflammation, facilitates phagosome-lysosome fusion

AMPK = adenosine monophosphate–activated protein kinase

Treating **TB infection** in people with diabetes

- In more than 23 randomized control trials, treatment of TB infection confers greater than 60% protection in preventing progression to active disease.
- There are no indications that individuals with diabetes will behave differently from others receiving treatment for TB infection, but this needs to be studied further with respect to optimal regimens and duration.

Sources. Smieja et al. 2000; Akolo et al. 2010; Ayieko et al. 2014; Riza et al. 2014; Ugarte-Gil et al. 2019

Summary

1. Diabetes is rising and this will affect our ability to eliminate TB
2. TB and diabetes work synergistically to cause immune dysfunction
3. Diabetes affects the ability of immune cells to function, resulting in unsuccessful treatment, death, or relapse.
4. Diabetes is associated with DR-TB in some studies, likely linked to inability to clear bacteria and increased time for mutation to develop.
5. How should this knowledge affect practice?
    - Search – continue to use x-ray, genetic tests, DST, and IGRA/TST
    - Treat – use standard treatments but think about treating the DM with metformin (which likely acts as an immunomodulator in addition to glycemic effects)
    - Prevent – diabetics appear to benefit as much as non-diabetics from preventive therapy

ZERO TB Initiative

Дякую
Рақмет сізге
Kiitos
Хвала вам
Gracias
Děkuju
Thank you
Ευχαριστώ
Mulțumesc
Благодаря ти
Спасибо
Hvala ti
Teşekkür ederim
Dank u
Obrigado
Grazie
Merci
Сипос
Danke

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