

# Exploring the double burden of tuberculosis and diabetes in the Republic of Moldova



**Master thesis** by Sophi Løge

MSc in Global Health

**Supervision by:** Dirk Lund Christensen, Anders Dejgaard & Ib Christian Bygbjerg

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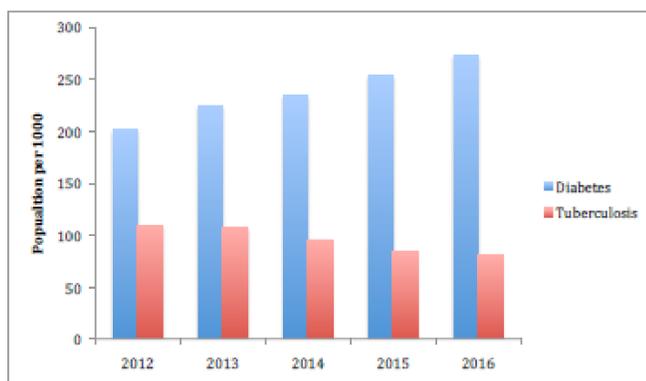
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## Introduction

The convergence of tuberculosis (TB) and diabetes mellitus (DM) is a global health concern. The high burden of TB remains pronounced in countries that experience a rapid escalation of DM, of which typically have weaker health system capacity to manage the two epidemics. DM increases the risk of developing TB and worsens disease outcomes. Reversely, TB creates a disease related hyperglycaemia response. Screening for the two diseases can intensify case detection, however the application of this has been challenged.

The Republic of Moldova is a small country located in South-Eastern Europe, landlocked between Romania and Ukraine. As like in many countries, the prevalence of DM is increasing (see *figure 1*).



**Figure 1:** Prevalence of DM and incidence of TB over time in the Republic of Moldova. Data from National Bureau of Statistics

While the incidence of TB has been decreasing in recent years, multidrug-resistant TB (MDR-TB) remains a challenge. The Global TB Report (2018) placed Moldova in the top 10 MDR-TB countries with the most severe burden in terms of incidence rates per capita.

The World Diabetes Foundation funded a project in Moldova screening DM in those with TB. It was intended to intensify detection of people with DM and TB, and to strengthen DM and TB collaboration in Moldova. The Association for Study of Chronic Diseases took on lead partnership in the project and data collection – of which lay the basis for the master thesis.

## Objectives

1. To estimate the proportion of DM and pre-DM in those with active TB, past TB and at risk for TB
2. To compare three glycaemia screening methods
3. To examine risk factors associated with screen detected DM in TB patients
4. To assess follow-up of DM screening in active TB patients

## Methodology

A prospective observational pragmatic project collected data from TB centres across different levels of the health system. This included regional TB outpatient clinics (*Dispensarul Ftiziopneumologic*), inpatient municipal hospitals, the National TB Institute's inpatient wards, and the TB medical facilities in the penitentiary system. See *figure 2* for project site locations.

### Inclusion criteria:

- Diagnosis with active TB, OR past TB (TB in anamnesis), OR in high vigilance/close contact to TB (family and healthcare workers)
- Age above 18 years
- Signature of informed consent

### Exclusion criteria:

- Mental disability

## Data

Demographic data and glycaemia measurements were collected between

January 2016 and December 2017.

Additional data were extracted from national registries, including: the National TB Registry (SIME-TB), the HIV registry, and narcological-use registry.

### Glycemia measurements collected:

- Fasting plasma glucose (FPG)
- Postprandial glucose (PPG)
- Glycated haemoglobin (HbA1c)

Follow-up FPG measurements were collected via FPG in active TB patients.

### Diagnostic criteria

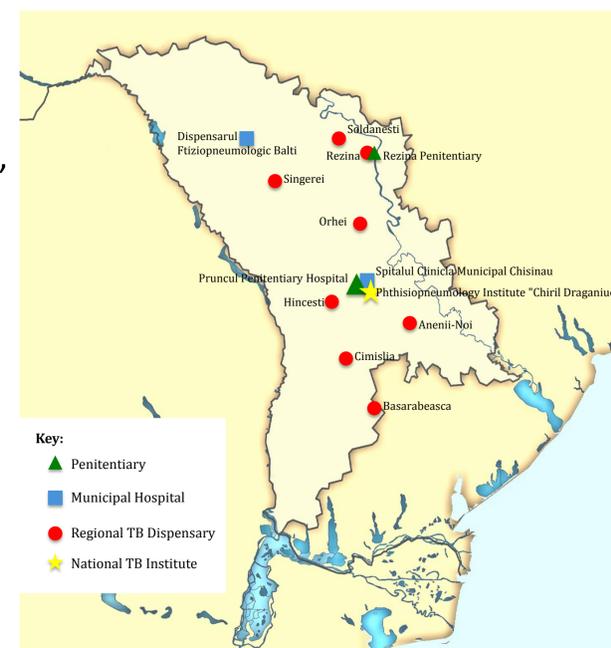
DM and pre-DM were classified by the WHO classifications for capillary blood samples and glycated haemoglobin recommendations.

### Statistics (SPSS)

- Cochran's Q test
- Pearson chi-squared tests
- McNemar chi-squared test
- Area under the receiver-operating characteristic (ROC) curve
- Binary logistic regressions to calculate odds ratios

### Ethics

The protocol for the project was approved by the Research Ethics Committee of IMSP Phtisiopneumology Institute "Chiril Draganiuc", with registration number CE-19.2.



**Figure 2:** Map of the Republic of Moldova with the location of project sites

## Key Results

A total of 2571 subjects were included in analyses in three groups: active TB (n = 1730), past TB (n = 356), and those at risk to TB (n = 485).

All subjects received a FPG test. Across all groups, 793 participants received all three glycaemia tests. The HbA1c test was performed in 35% of the total sample, and predominantly in the active TB group. *Table 1* depicts the number of participants in each group and how many subjects received each glycemia test.

**Table 1:** Number of study participants receiving glycaemia tests per group

Test Type	Number of participants			Overall number of participants
	Active TB	Past TB	At risk	
<b>First test</b>				
FPG	1730	356	485	2571
PPG	1603	341	457	2401
HbA1c	647	40	213	900
<b>Follow-up test</b>				
FPG	462	27	44	533
PPG	435	27	42	504
HbA1c	28	1	15	44

## 1 Diabetes and Pre-Diabetes Prevalence

Overall 369 (14.3%) participants were diagnosed with DM by any glycaemia test. The prevalence of diabetes in the total sample was 6.9% by FPG, 3.3% by PPG and 26.6% by HbA1c tests. There was a statistical significant difference between the proportions of these three tests (Cochran's Q = 301.19 (2), p < 0.001).

Furthermore, 11.9% of the sample was classified with pre-DM by FPG, 15.5% by PPG, and 38.9% by HbA1c.

In the subsample of participants (n = 115) from the penitentiary system, 20.9% were diagnosed with DM by FPG and 11.7% by the HbA1c test.

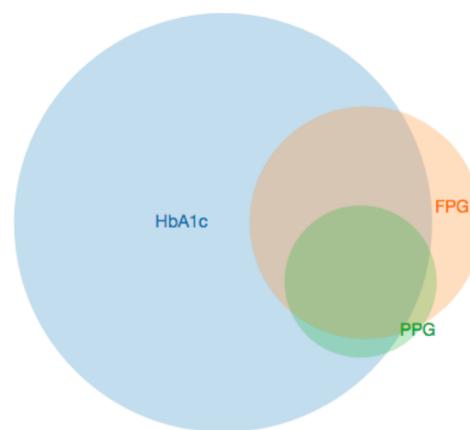
Between group Pearson chi-squared analysis revealed both the active and at risk TB groups had a significantly higher diabetes prevalence (7.2% and 7.8%) by FPG than the past TB group (4.2%) ( $\chi^2 = 4.29$ ,  $df = 1$ ,  $p = 0.038$ ;  $\chi^2 = 4.56$ ,  $df = 1$ ,  $p = 0.033$ , respectively).

There were fewer statistically different proportions of diabetes classifications between groups when HbA1c was measured. It was only the active TB group that has a significantly lower proportion of diabetes (24.4%) as compared to the at risk TB group (32.9%) ( $\chi^2 = 5.86$ ,  $df = 1$ ,  $p = 0.015$ ).

## 2 Comparison of three glycaemia tests

On the right is a Venn diagram of the participants who were diagnosed with diabetes AND had all 3 glycaemia tests administered. It can be seen that HbA1c detected most of participants with diabetes, with a large overlap with FPG and PPG tests.

The area under the ROC curve for FPG and PPG demonstrated lower diagnostic accuracy when compared against cases with a DM diagnosis by HbA1c.



**Figure 3:** Venn diagram depicting DM diagnosis by glycemia test

## 3 Risk Factors associated with diabetes among TB participants

Significant risk factors associated with screen detected DM were found to have the following Odds Ratios, identified by logistic regression:

Age 65+ years, 3.0 (p = 0.008), compared to younger participants

Male, 1.45 (p = 0.036), compared to females

Alcohol use, 0.52 (p = 0.02), compared to non identified alcohol use by narcologist

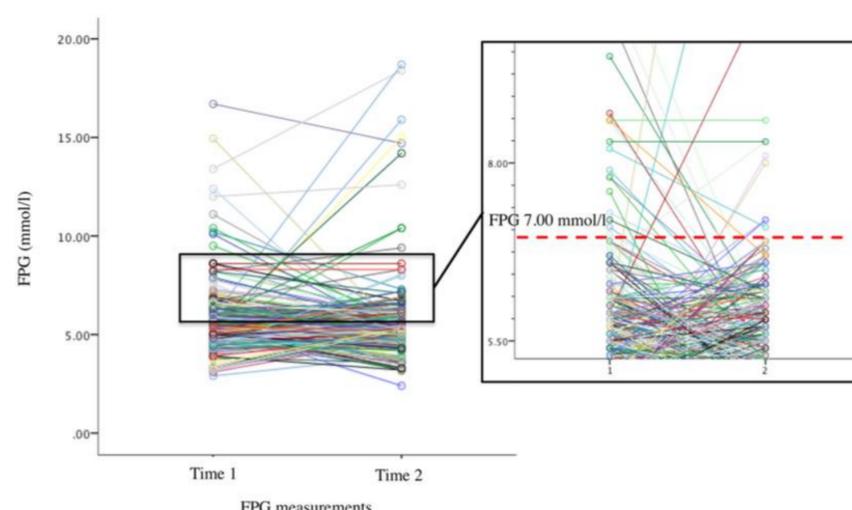
MDR-TB, 1.82 (p < 0.001), compared to non MDR-TB participants

## 4 Follow-up diabetes prevalence

Overall 438 participants had follow-up FPG measurements with more than 1 month between the two points of data collection. The average time between follow-up glycaemia measurements was 3.63 months (SD = 2.30), with a range from 1-18 months. Most of the participants in follow-up (86.1%) were in the active TB group.

There was no statistical difference between the prevalence of DM and pre-DM between time one and time two by McNemar's test. Therefore there is no evidence of diabetes improving or worsening over TB in this data.

A Spaghetti diagram depicted to the right shows the two FPG measurements (in mmol/l), and an enlargement of the diabetes cutoff (7.0 mmol/l). Both of these graphs show that there was no major increase or decrease in FPG concentrations over time.



**Figure 4:** Spaghetti diagram depicting FPG measurements in those with active TB over time

## Points for discussion

To my knowledge these are the first data exploring the double burden of DM and TB in the Republic of Moldova. These are also the first to screen three groups of TB for DM across all levels of the health system and spread across a wide geographical area. With this reach and the large sample size of 2571 included in analyses, it is possible to generalize the determined results.

- The prevalence of DM and pre-DM found in this sample are consistent with systematic reviews and meta-analyses including studies that have screened for DM in TB subjects (Jeon et al., 2010, Workneh et al., 2017). Many of these past studies are limited in describing the significance of the DM-TB comorbidity in local contexts, as study designs lack a control or comparison group. Therefore a strength in these data are findings comparing the at risk group.
  - Between group comparisons among the At risk TB group and the active TB group identified no statistically significant differences in DM prevalence by FPG and PPG measurements, but a significant difference by HbA1c measurement. DM prevalence by HbA1c were higher in the at risk group (32.9%) compared to the active TB group (24.4%). This study lacks data identifying factors that may be related to this difference, however these findings substantiate the results in showing Moldova as a context with a high DM prevalence.
- These data are among few in the literature that compare three screening methods of DM in TB. It is possible however, that the higher diagnostic accuracy of HbA1c and FPG, when compared against DM cases identified by PPG, can be attributed to reasons beyond glycemic test accuracy. The HbA1c machine was only available in in-patient wards treating the “sickest” TB patients, inducing a selection bias in those screened by HbA1c. In addition, there was no standard meal controlling for carbohydrate/glucose intake in the PPG test. Despite these limitations to the pragmatic design of the study, these data provide insight to support decisions on identifying an accurate glycemic test for screening DM in TB subjects.
- Risk factors identified in the data depict a “phenotype” of TB subject characteristics’ to having screen detected (not previous) DM. More rigorous data in demographic characteristics (eg: family history of diabetes, socioeconomic status, education level etc.) and health behaviours (eg: smoking frequency and alcohol consumption) are required to ensure the results as concrete risk factors for a TB subject to develop DM.
- Previously published prospective data following glycemia across TB treatment are limited and vary in their determined results. Some of these data are consistent with a theory of *Stress Hyperglycemia*, in that hyperglycemia is caused by a physiological condition of stress induced by the TB diseased state. This theory proposes that DM should reduce over the course of TB treatment. These data did not show any significant differences between glycemia time points, therefore not supporting this physiological theory. However, to test this theory in greater detail rigorous time points of retesting should be integrated into the study design.

## Acknowledgement

I would like to extend a very special thank you to the World Diabetes Foundation for the opportunity to participate in this project. Also to the hard working team members in Moldova who not only accomplished a great task collecting this comprehensive data, but also who generously took time to show me their country .

**Figure 5:** The team on visit in Moldova, April 2018  
From right: Kirza Buch Kristensen (WDF\*), Elsa Morandat (WDF\*), Sophi Løge (master thesis student) and Natalia Palaire (ASCD\*\*)

\* World Diabetes Foundation

\*\* Association for Study of Chronic Diseases



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