Early View

Research letter

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Dysglycaemia among tuberculosis patients without known diabetes in a low-endemic setting

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To the editor:

There is increasing evidence that diabetes mellitus (DM) is an important risk factor for tuberculosis (TB) and might affect TB-disease presentation as well as treatment response ¹. The theory is that an impaired immune response in persons with DM facilitates infection with *Mycobacterium tuberculosis* (*Mtb*) and/or progression to TB and reversely, *Mtb* infection may affect the glycaemic control ^{2,3}. Although the exact causality is unknown, this association between TB and DM is ominous, as the explosive rise in DM worldwide witnessed over the last decades could potentially counteract the positive effect of TB control efforts.

Denmark is a low incidence country for TB with an incidence rate of 5.0 per 100,000 population ⁴. The prevalence of DM is 4.8% and 4.0-6.9% have prediabetes (pre-DM) ^{5,6}. We have currently reported a prevalence of known DM before TB diagnosis of 5.0% ⁷, but the extent of dysglycaemia and undiagnosed DM in TB-patients is unknown. The objective of this study was to investigate the

burden of undiagnosed DM and dysglycaemia among TB-patients and risk factors hereof in a low-endemic setting.

We conducted a retrospective cohort study at the TB outpatient-clinic at Copenhagen University Hospitals, Herlev-Gentofte, Denmark. All registered TB-patients ≥ 18 years starting anti-TB-treatment in the period April 1st 2018 through July 1st 2020 were included. Haemoglobin A1c (HbA1c) was implemented as part of the routine blood sampling when starting anti-TB-treatment on April 1st 2018. Patients were excluded if HbA1c was not measured within one week before and one week after starting anti-TB-treatment.

Data on comorbidities, patient reported country of origin, alcohol, tobacco and/or drug use and blood test results were retrospectively collected from patient files. Patients were defined as having known DM if they had an ICD-10 DM-diagnosis (E08-E13) and/or received anti-diabetic treatment. Patients were defined as having dysglycaemia if HbA1c ≥ 39 mmol/mol ($\geq 5.7\%$), pre-DM if HbA1c 39-47 mmol/mol (5.7-6.4%) and DM if HbA1c ≥ 48 mmol/mol ($\geq 6.5\%$), according to the American Diabetes Association's guidelines ⁸.

Frequencies, rates and prevalences were estimated. Fishers test and Wilcoxon signed-rank test for comparing independent groups were performed as appropriate. Poisson regression was used to estimate unadjusted and adjusted odds ratios (OR) and their respective 95% confidence interval. Level of significance was set at 5%. Data was analysed using R Studio.

The study was approved by The Danish Patient Safety Authority (J nr: 31-1521-460) and The Danish Data Protection Agency (P-2020-838). The study required no Ethics Committee approval.

Results showed that 188 TB-patients were registered with a TB-diagnosis of whom 121 had HbA1c tested at baseline. Eleven (9.2%) had previously known DM and were excluded from risk factor analysis. Of the remaining 110 patients, 30 (27.3%) had pre-DM (HbA1c ≥ 39 mmol/mol) and two (1.8%) had DM (HbA1c > 48 mmol/mol). We calculated numbers needed to screen with HbA1c to find one case of either pre-DM or DM at time of TB-diagnosis to be 4 and 56, respectively.

TB-patients with dysglycaemia were significantly older than patients with normal HbA1c (median age 54 vs. 42 years, $p=0.005$) and more were male (84.4 vs. 50.0%, $p=0.001$). No difference was found in smoking, alcohol and drug use, BMI, or comorbidities. Dysglycaemia was positively associated with multifocal (18.8 vs 2.6%, $p=0.007$) and cavernous disease (50.0 vs 17.0%, $p=0.020$).

Dysglycaemia was found in 23.1% (12/52) of the TB-patients originating from Denmark, 36.4% (8/22) from Greenland, 27.8% (5/18) from Asia, 57.1% (4/7) from Africa, 50% (3/6) from Europe outside Denmark and 0% (0/5) from the Middle East.

Regression analyses (table 1) found age >40 years and male sex significantly associated with higher risk of dysglycaemia (OR 5.6 [1.9; 20.9], $p=0.004$ and 4.6 [1.7; 14.9], $p=0.006$, respectively).

Originating from another country than Denmark or Greenland was associated with a significantly higher risk when stratified for age and gender (OR 5.9 [1.7; 24.2], $p=0.009$).

The pre-DM prevalence of 27.3% among TB-patients is comparable to prevalence seen in TB patients from DM high endemic areas such as India of 33%⁹. The estimated background prevalence of pre-DM in Denmark is 4.0-6.9%⁶, albeit, defined by an HbA1c of 42-47 mmol/mol. By including only those TB-patients with HbA1c > 42 mmol/mol, the prevalence in our study was still 2-3 times as high as the estimated background prevalence (11.8%).

Dysglycaemia was not surprisingly associated with male gender and older age, equivalent to results from other studies⁹⁻¹¹. As expected, we found high prevalences of dysglycaemia in persons from DM high endemic regions; similar to the findings in our recent Danish register study⁷. Interestingly, in our register study we found no previously known DM among TB-patients from Greenland, while 36.4% of Greenlanders in the present study were dysglycaemic. Given the incidence of DM in Greenland is high and increasing¹², it was surprising to find no patients with DM in the register study. The discrepancy could potentially be explained by underdiagnosing of DM among Greenlanders with TB in Denmark; Greenlanders diagnosed with TB in Denmark are often part of a socially marginalised group, many struggle with alcohol abuse and might not consult their doctor, leading to underdiagnosed DM¹³. Additionally, HbA1c testing of TB-patients has not previously been routine in Denmark, therefore pre-DM was not estimated in the register study.

Significantly more patients with dysglycaemia had more than one TB localisation and caverns as a sign of high disease burden, supporting the hypothesis that dysglycaemia is associated with disease presentation^{9,10}. It is however, unknown whether the *Mtb* infection tend to worsen the glycaemic control or if hyperglycaemia facilitates severe TB.

The TB-patients that were excluded due to lack of HbA1c were slightly younger (median age 40 vs. 48 years, $p=0.030$), more came from outside Denmark (67.2 vs. 52.7%, $p=0.080$) and more of the excluded patients with pulmonary TB had caverns (36.7 vs. 26.9%, $p=0.470$). As the risk of DM and dysglycaemia was found to increase with age, was more frequent among persons born outside Denmark and was associated with severe TB, we may have over- or underestimated the prevalence of dysglycaemia by excluding these TB-patients.

Timing of baseline blood tests varied up to one week before and after initiation of anti-TB treatment but as HbA1c is a proxy for blood glucose over three months, we consider our results to present a

reliable estimate of dysglycaemia. Our results emphasise that TB-patients are at risk of dysglycaemia even in a low endemic setting of both TB and DM. We do not have data on treatment outcome or HbA1c development during treatment but studies indicate that glycaemic control often is restored after anti-TB-treatment ^{3,11,14}. Follow-up with systematic testing of HbA1c would be relevant to distinguish whether our TB-patients have transient dysglycaemia or actual DM/Pre-DM.

In conclusion, this study highlights the importance of co-management of TB and DM, as many patients without known DM are dysglycaemic and as untreated dysglycaemia can lead to long-term complications. Many TB-patients in Denmark struggle with social problems and language barriers that might delay consulting a doctor; DM screening of this population is therefore an excellent opportunity for early diagnosis of DM and intervention in those at high risk of long-term complications. Based on this study, we strongly support the concept of integrated management of TB and DM, even in TB and DM low-endemic settings ¹⁴.

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	Crude analysis		Multivariate analysis*	
Risk factor	OR [95% CI]	p-value	OR [95% CI]	p-value
Age				
Age ≤ 40 years	1 (Ref)	-	1 (Ref)	-
Age > 40 years	6.3 [2.2; 22.8]	0.002	5.6 [1.9; 20.9]	0.004
Sex				
Female	1 (Ref)	-	1 (Ref)	-
Male	5.4 [2.0; 17.2]	0.002	4.6 [1.7; 14.9]	0.006
Substance use				
No history of excessive alcohol intake	1 (Ref)	-	1 (Ref)	-
History of excessive alcohol intake	2.4 [1.0; 5.6]	0.044	2.0 [1.0; 5.1]	0.138
No history of smoking	1 (Ref)	-	1 (Ref)	-
Previous or current smoker	1.7 [0.7; 4.4]	0.271	0.6 [0.2; 1.9]	0.396
No history of drug use	1 (Ref)	-	1 (Ref)	-
History of drug use	1.0 [0.4; 2.4]	0.994	1.1 [0.4; 3.1]	0.862
Region of origin				
Denmark	1 (Ref)	-	1 (Ref)	-
Greenland	1.9 [0.6; 5.6]	0.243	3.6 [1.0; 14.6]	0.056
Immigrants**	1.3 [0.6; 3.2]	0.495	5.9 [1.7; 24.2]	0.009
Disease presentation				
Pulmonary TB	1 (Ref)	-	1 (Ref)	-
Extra-pulmonary TB	0.2 [0.0; 1.1]	0.123	0.3 [0.0; 1.7]	0.234
Disseminated TB***	7.5 [1.6; 54.0]	0.017	10.6 [1.8; 91.5]	0.013
No caverns****	1 (Ref)	-	1 (Ref)	-
Caverns****	4.8 [1.8; 13.3]	0.002	5.3 [1.8; 17.2]	0.003

Abbreviations: CI, confidence interval; HbA1c, Haemoglobin A1c; OR, odds ratio; TB, tuberculosis.

* Adjusted for age, sex, not including the measured risk factor.

**Defined as all patients not born in Denmark or Greenland.

***Defined as more than one TB location, including military TB.

****In patients with pulmonary TB.