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

Received: 8 Nov 2021
Accepted: 5 Jan 2022

To the Editor:

There is increasing evidence that diabetes mellitus is an important risk factor for tuberculosis (TB) and might affect TB-disease presentation as well as treatment response [1]. The hypothesis is that an impaired immune response in persons with diabetes mellitus facilitates infection with *Mycobacterium tuberculosis* and/or progression to TB, and reversely, *M. tuberculosis* infection may affect glycaemic control [2, 3]. Although the exact causality is unknown, this association between TB and diabetes mellitus is ominous, as the explosive rise in diabetes mellitus 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 diabetes mellitus is 4.8% and 4.0–6.9% have prediabetes [5, 6]. We have reported a prevalence of known diabetes mellitus before TB diagnosis of 5.0% [7] but the extent of dysglycaemia and undiagnosed diabetes mellitus in TB patients is unknown. The objective of this study was to investigate the burden of undiagnosed diabetes mellitus and dysglycaemia among TB patients, and risk factors thereof, 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 old starting anti-TB treatment in the period 1 April 2018 to 1 July 2020 were included. Haemoglobin A1c (HbA1c) was implemented as part of the routine blood sampling when starting anti-TB treatment on 1 April 2018. Patients were excluded if HbA1c was not measured within 1 week before and 1 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 diabetes mellitus if they had an International Classification of Diseases (10th revision) diabetes mellitus diagnosis (E08–E13) and/or received anti-diabetic treatment. Patients were defined as having dysglycaemia if HbA1c was ⩾39 mmol·mol^{-1} (⩾5.7%), prediabetes if HbA1c was 39–47 mmol·mol^{-1} (5.7–6.4%) and diabetes mellitus if HbA1c was ⩾48 mmol·mol^{-1} (⩾6.5%), according to the American Diabetes Association's guidelines [8].

Frequencies, rates and prevalences were estimated. Fisher's test and the Wilcoxon signed-rank test for comparing independent groups were performed as appropriate. Poisson regression was used to estimate unadjusted and adjusted odds ratios and their respective 95% confidence intervals. The level of significance was set at 5%. Data were 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. 11 (9.2%) had previously known diabetes mellitus and were excluded from risk factor analysis. Of the remaining 110 patients, 30 (27.3%) had prediabetes (HbA1c ⩾39 mmol·mol^{-1}) and two (1.8%) had

Shareable abstract (@ERSpublications)
With a high prevalence of dysglycaemia (29.1%) among tuberculosis patients without previously known diabetes, this study highlights the importance of comanagement of tuberculosis and diabetes, even in a low-endemic setting https://bit.ly/3Gj0gmN

Cite this article as: Jørgensen A, Lorentsson HJN, Grundtvig Huber F, *et al*. Dysglycaemia among tuberculosis patients without known diabetes in a low-endemic setting. *ERJ Open Res* 2022; 8: 00629-2021 [DOI: 10.1183/23120541.00629-2021].

diabetes mellitus (HbA1c >48 mmol·mol^{-1}). We calculated numbers needed to screen with HbA1c to find one case of either prediabetes or diabetes mellitus at time of TB diagnosis to be four and 56, respectively.

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

Dysglycaemia was found in 23.1% (12 out of 52) of the TB patients originating from Denmark, 36.4% (eight out of 22) from Greenland, 27.8% (five out of 18) from Asia, 57.1% (four out of seven) from Africa, 50% (three out of six) from Europe outside Denmark and 0% (none out of five) 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 (95% CI 1.9–20.9, p=0.004) and 4.6 (95% CI 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 sex (OR 5.9, 95% CI 1.7–24.2; p=0.009).

The prediabetes prevalence of 27.3% among TB patients is comparable to prevalence seen in TB patients from diabetes mellitus high-endemic areas such as India, of 33% [9]. The estimated background prevalence of prediabetes in Denmark is 4.0–6.9% [6], albeit defined by an HbA1c of 42–47 mmol·mol^{-1}. By including only those TB patients with HbA1c >42 mmol·mol^{-1}, the prevalence in our study was still two to three times as high as the estimated background prevalence (11.8%).

Dysglycaemia was, not surprisingly, associated with male sex and older age, equivalent to results from other studies [9–11]. As expected, we found high prevalences of dysglycaemia in persons from diabetes mellitus high-endemic regions, similar to the findings in our recent Danish register study [7]. Interestingly, in our register study, we found no previously known diabetes mellitus among TB patients from Greenland, while 36.4% of Greenlanders in the present study were dysglycaemic. Given the incidence of diabetes

TABLE 1 Univariate and multivariate regression analyses for risk factors of having HbA1c ⩾39 mmol·mol^{-1} at the time of tuberculosis (TB) diagnosis

Risk factor	Crude analysis		Multivariate analysis[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				
⩽40 years	1 (ref.)		1 (ref.)	
>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
Immigrant[¶]	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 cavitations[§]	1 (ref.)		1 (ref.)	
Cavitations[§]	4.8 (1.8–13.3)	0.002	5.3 (1.8–17.2)	0.003

[#]: adjusted for age and sex, not including the measured risk factor; [¶]: all patients not born in Denmark or Greenland; [+]: more than one TB location, including military TB; [§]: in patients with pulmonary TB.

mellitus in Greenland is high and increasing [12], it was surprising to find no patients with diabetes mellitus in the register study. The discrepancy could potentially be explained by underdiagnosing of diabetes mellitus 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 diabetes mellitus [13]. Additionally, HbA1c testing of TB patients has not previously been routine in Denmark; therefore, prediabetes was not estimated in the register study.

Significantly more patients with dysglycaemia had more than one TB localisation and cavitations 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 *M. tuberculosis* infection tends to worsen the glycaemic control or if hyperglycaemia facilitates severe TB.

The TB patients that were excluded due to lack of HbA1c data were slightly younger (median age 40 *versus* 48 years, p=0.030), more came from outside Denmark (67.2% *versus* 52.7%, p=0.080) and more of the excluded patients with pulmonary TB had cavitations (36.7% *versus* 26.9%, p=0.470). As the risk of diabetes mellitus 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 by up to 1 week before and after initiation of anti-TB treatment but as HbA1c is a proxy for blood glucose over 3 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 diabetes mellitus. 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, actual diabetes mellitus or prediabetes.

In conclusion, this study highlights the importance of co-management of TB and diabetes mellitus, as many patients without known diabetes mellitus 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; diabetes mellitus screening of this population is therefore an excellent opportunity for early diagnosis of diabetes mellitus 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 diabetes mellitus, even in TB and diabetes mellitus low-endemic settings [14].

Anja Jørgensen [1,2], Hans Johan Niklas Lorentsson[1,3], Franziska Grundtvig Huber[1], Sidse Graff Jensen[4], Karen Bjorn-Mortensen[1] and Pernille Ravn[1]

[1]Dept of Medicine, Unit of Infectious Diseases, Copenhagen University Hospitals Herlev and Gentofte, Herlev and Gentofte, Denmark. [2]International Reference Laboratory of Mycobacteriology at Statens Serum Institut, Copenhagen, Denmark. [3]Steno Diabetes Centre, Copenhagen, Denmark. [4]Dept of Medicine, Unit of Respiratory Medicine, Copenhagen University Hospitals Herlev and Gentofte, Herlev and Gentofte, Denmark.

Corresponding author: Anja Jørgensen (anjj@ssi.dk)

Provenance: Submitted article, peer reviewed.

Conflict of interest: None declared.

References

1 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008; 5: e152.

2 Kumar Nathella P, Babu S. Influence of diabetes mellitus on immunity to human tuberculosis. *Immunology* 2017; 152: 13–24.

3 Boillat-Blanco N, Ramaiya KL, Mganga M, *et al.* Transient hyperglycemia in patients with tuberculosis in Tanzania: implications for diabetes screening algorithms. *J Infect Dis* 2016; 213: 1163–1172.

4 Statens Serum Institut. Epi-Nyt. www.ssi.dk/aktuelt/nyhedsbreve/epi-nyt/2019/uge-37---2019 Date last updated: 11 September 2019.

5 Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. *BMJ Open Diabetes Res Care* 2020; 8 :e001071

6 Jørgensen ME, Ellervik C, Ekholm O, *et al.* Estimates of prediabetes and undiagnosed type 2 diabetes in Denmark: the end of an epidemic or a diagnostic artefact? *Scand J Public Health* 2020; 48: 106–112.

7 Huber FG, Kristensen KL, Holden IK, *et al.* The prevalence of diabetes among tuberculosis patients in Denmark. *BMC Infect Dis* 2022; 22: 64.

8 Kumar R, Nandhini LP, Kamalanathan S, *et al.* Evidence for current diagnostic criteria of diabetes mellitus. *World J Diabetes* 2016; 7: 396–405.

9 Mave V, Meshram S, Lokhande R, *et al.* Prevalence of dysglycemia and clinical presentation of pulmonary tuberculosis in Western India. *Int J Tuberc Lung Dis* 2017; 21: 1280–1287.

10 Barreda NN, Arriaga MB, Aliaga JG, *et al.* Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia. *BMC Infect Dis* 2020; 20: 139.

11 Tabarsi P, Baghaei P, Marjani M, *et al.* Changes in glycosylated haemoglobin and treatment outcomes in patients with tuberculosis in Iran: a cohort study. *J Diabetes Metab Disord* 2014; 13: 123.

12 Juel K, Davidsen M, Pedersen PV, *et al.* Socialt Udsattes Brug af Sundhedsvæsenet [Healthcare Use by the Socially Disadvantaged]. Copenhagen, Rådet for Socialt Udsatte, 2010.

13 Rådet for Socialt Udsatte. “I Grønland er Jeg For Dansk, og i Danmark er Jeg ‘Bare’ Grønlænder” [“In Greenland, I am too Danish, and in Denmark, I am ‘just’ a Greenlander”]. Copenhagen, Rådet for Socialt Udsatte, 2016.

14 Harries AD, Kumar AMV, Satyanarayana S, *et al.* Diabetes mellitus and tuberculosis: programmatic management issues. *Int J Tuberculosis Lung Dis* 2015; 19: 879–886.