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Low prevalence of diabetes mellitus among tuberculosis patients and their community in urban Uganda

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Dear Editor,

Globally, epidemics of diabetes mellitus (DM) and tuberculosis (TB) are increasingly linked.[1,2] Diabetes is associated with TB infection and with a two-to-four-fold increase in the risk of active disease;[3] active TB may also increase the risk of diabetes.[4] In sub-Saharan Africa, where the prevalence of diabetes in the general population is lower than in other regions,[5] the prevalence of diabetes among patients with TB has been estimated at 9%.[6] However, many studies that contributed to that estimate, including one in Uganda,[7] evaluated only hospitalized TB patients and may not be representative of the region's TB epidemic as a whole. There are few data from sub-Saharan African settings on the prevalence of DM among non-hospitalized TB patients or people with TB who have not yet sought treatment. Therefore, the extent to which diabetes detection or management should be integrated with TB care in this region remains unclear.

We used a TB case-finding study as an opportunity to estimate the prevalence of diabetes among people with and without TB in a community of Kampala, Uganda. We recruited adult (>15 years) TB cases and TB-negative controls from health facilities and the community. The health facility component recruited patients who were diagnosed with TB by any method at four local facilities ("health-facility cases") and a representative sample of

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individuals with negative TB evaluations in the same facilities (“health-facility controls”, two per case) from May 2018 to April 2020. The community-based component, from February 2019 to December 2019, involved sputum Xpert MTB/RIF Ultra testing for all consenting adult residents of the study community. Individuals diagnosed with TB through active case finding were enrolled as “community cases”, and a sample of Xpert-negative individuals matched by zone of residence were enrolled as “community controls” (one for each case of either type enrolled during this period).

Hemoglobin A1c (HbA1c) testing was conducted for cases and controls enrolled from May 2018-February 2019, July-December 2019, and January-April 2020. Testing was performed with a Eurolyzer Cube (Diagnostica GmbH, Salzburg Austria) on 2ml venous blood samples. Participants provided informed consent for all procedures, and the Makerere University College of Health Sciences Institutional Review Board approved the study.

We estimated the prevalence of diabetes (HbA1c ≥48 mmol/mol [≥6.5%]), and prediabetes (HbA1c 42-47 mmol/mol [6.0-6.4%]). We compared diabetes prevalence and demographic characteristics between cases and controls and by enrollment method (health facility vs. community).. We also calculated the population attributable fraction (PAF) of tuberculosis attributable to DM, using the prevalence of diabetes among all controls to estimate population diabetes prevalence and the odds ratio among all cases versus all controls to estimate relative risk.[9] All analyses were conducted using STATA version 16.

Of 711 participants eligible for HbA1c testing, 491 (69%) were tested; reasons for not testing include refusal (n=6), materials/device not available (n=139), and other/unknown (n=75).. Overall, 238 (48%) participants were male, and the median age was 30 (IQR 24-40). HIV prevalence was 30% (n=148). Fourteen individuals (2.9%) had an HbA1c result consistent with diabetes (median 58 mmol/mol, IQR 52-85 mmol/mol). Of these, 5 (36%) had a previous diabetes diagnosis, as did one participant with a normal HbA1c.

The prevalence of diabetes was higher among individuals age ≥45 years (10.3%, 95%CI 4.8-18.7%) compared to younger individuals (1.2%, 0.4-2.9%), with similar prevalence among older TB cases (12.1%, 3.4-28.2%) and older TB-negative individuals (9.3%, 3.1-20.3%). Among those with height and weight measured (n=453), the prevalence of diabetes was 6.4% (95%CI 1.5-23.4%) among those categorized as obese, 5.4% (95%CI 2.0-13.7%) among the overweight, 2.8% (95%CI 1.3-5.8%) among those of normal weight, and 4.0% (95%CI 1.5-10.4%) among the underweight.

The prevalence of diabetes was similar in health facility cases (3.8%, 95% CI 1.2-8.6%) and controls (3.4%, 95%CI 1.4-6.8%) (Table 1). In the community, very little diabetes was found, with no diabetes among community cases (95% CI for prevalence 0-0.8%) and 2 cases among community controls (2.1%, 95%CI 0.26-7.4%). The estimated odds ratio for the association of diabetes and TB case status was 0.9 (95%CI 0.30-2.7), yielding a PAF estimate with an upper bound of the 95% confidence interval of 2.9%.

The prevalence of diabetes in our study population overall (2.9%) and our community control population in particular (2%) was similar to the prevalence of diabetes reported for the general population in Uganda (1.4%).[10] The prevalence of diabetes in our health facility

cases (3.8%) is also consistent with a larger study of TB patients in an outpatient setting in Kampala which found a 2.3% prevalence of diabetes.[11] Notably, studies of hospitalized patients from Uganda[7] and elsewhere in sub-Saharan Africa[12] have reported a much higher prevalence of diabetes – but these estimates may not reflect the burden of diabetes in the underlying community. While our estimate of overall diabetes prevalence is consistent with other studies in Uganda, our results may not reflect the contribution of diabetes to TB in Uganda as a whole, due to the young age distribution in the study population and the younger average age of individuals with prevalent compared to notified TB. Furthermore, although the number of community cases who underwent A1c testing was small, we found no diabetes in this group, suggesting that diabetes is not a driver of subclinical or undiagnosed TB in this study.

Although our estimate of the association between TB and diabetes has an upper bound (odds ratio 2.7) that would be consistent with estimates from other settings,[1] our findings suggest that diabetes is a weaker risk factor for TB in our study population. This discrepancy may be due to a lower prevalence of factors that predispose to diabetes, such as obesity and advanced age, and a higher prevalence of certain TB risk factors such as HIV infection and undernutrition, in African settings than in many other areas of the world.[13] A limitation of our study is the small number of participants with diabetes in this population. However, the 2.9% upper bound on the estimated population attributable fraction suggests that DM plays a small role, if any, in sustaining the TB epidemic in this setting.

In conclusion, the prevalence of diabetes among people tested for TB in urban Uganda was low and not associated with TB status among either patients presenting at health facilities or participants in community-based TB screening. As a result, no more than 3% of TB cases at the population level were attributable to diabetes in this setting. While diabetes screening, treatment and TB prevention are important for the small fraction of the population (and larger fraction of older individuals) who have diabetes, diabetes management and prevention are unlikely to have large effects on population-level TB incidence in settings such as Kampala.

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Table 1:

Characteristics of people with TB (cases) and TB-negative controls identified from health facilities and the community in an urban setting in Kampala, Uganda.

Characteristics	Health Facility cases (n=132)	Health Facility controls (n=209)	Community Cases (n=55)	Community Controls (n= 95)
Sex				
Female	51 (39%)	123 (59%)	21 (38%)	58 (61%)
Male	81 (61%)	86 (41%)	34 (62%)	39 (39%)
Median Age in years (IQR)	32 (26-41)	33 (24-43)	28 (24-35)	27 (21-35)
HIV				
Positive	60 (46%)	73 (35%)	7 (13%)	8 (8%)
Negative	72 (55%)	136 (65%)	48 (87%)	87 (92%)
Self-reported asthma or COPD	1 (1%)	2 (1%)	0 (0%)	2 (2%)
Self-reported hypertension	1 (1%)	9 (4%)	1 (2%)	2 (2%)
Self-reported smoking (current or history of at least 100 cigarettes or equivalent)	43 (33%)	41 (20%)	11 (20%)	8 (8%)
Median HbA1c (IQR), mmol/mol	29 (24-36)	30 (24-36)	27 (23-36)	29 (24-36)
Diabetes prevalence				
Diabetes	5 (3.8%)	7 (2.4%)	0	2 (2.1%)
Prediabetes	8 (6.1%)	5 (2.4%)	2 (3.6%)	6 (6.3%)
WHO BMI classification				
Underweight	56 (43%)	24 (12%)	12 (23%)	7 (12%)
Normal weight	63 (48%)	119 (57%)	34 (65%)	33 (54%)
Overweight	10 (8%)	45 (22%)	5 (10%)	14 (23%)
Obese	2 (2%)	21 (10%)	1 (2%)	7 (12%)
Missing	1 (0.8%)	0 (0%)	3 (5.5%)	34 (36%)