

Brief Original Article

## Glycated hemoglobin screening identifies patients admitted for retreatment of tuberculosis at risk for diabetes in Tanzania

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### Abstract

**Introduction:** World Health Organization recommendations of bidirectional screening for tuberculosis (TB) and diabetes have been met with varying levels of uptake by national TB programs in resource-limited settings.

**Methodology:** Kibong'oto Infectious Diseases Hospital (KIDH) is a referral hospital for TB from northern Tanzania, and the national referral hospital for multidrug-resistant (MDR)-TB. Glycated hemoglobin (HgbA1c) testing was done on patients admitted to KIDH for newly diagnosed TB, retreatment TB, and MDR-TB, to determine the point prevalence of diabetes (HgbA1c  $\geq$  6.5%) and prediabetes (HgbA1c 5.7%–6.4%).

**Results:** Of 148 patients hospitalized at KIDH over a single week, 59 (38%) had no prior TB treatment, 22 (15%) were retreatment cases, and 69 (47%) had MDR-TB. Only 3 (2%) had a known history of diabetes. A total of 144 (97%) had successful screening, of which 110 (77%) had an HgbA1c  $\leq$  5.6%, 28 (19%) had  $\geq$  5.7 < 6.5, and 6 (4%) had  $\geq$  6.5. Comparing subjects with prediabetes or diabetes to those with normal A1c levels, retreatment patients were significantly more likely to have a A1c  $\geq$  5.7% (odds ratio: 3.2, 95% CI: 1.2–9.0;  $p = 0.02$ ) compared to those without prior TB treatment. No retreatment case was a known diabetic, thus the number needed to screen to diagnose one new case of diabetes among retreatment cases was 11.

**Conclusions:** Diabetes prevalence by HgbA1c was less common than expected, but higher HgbA1c values were significantly more frequent among retreatment cases, allowing for a rational, resource-conscious screening approach.

**Key words:** multidrug-resistant tuberculosis; diabetes; hemoglobin A1c; point-of-care.

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### Introduction

Diabetes is a risk factor for active tuberculosis (TB), with meta-analyses estimating that patients with diabetes are about three times more likely than those without to develop TB [1,2]. In the setting of TB disease, patients with diabetes have worse treatment outcomes, including, in some studies, a higher mortality compared to non-diabetics when controlling for other co-morbidities [3-6]. Consequent efforts to screen for diabetes among TB patients has found varying rates of new diabetes cases, ranging from 2%–35%, depending on the population of study [7]. For instance, the number of TB patients needed to screen (NNS) to identify one new case of diabetes in Kerala, India was only four [8].

Subsequent recommendations by the World Health Organization (WHO) to study implementation strategies of bidirectional screening for TB and diabetes have been met with varying levels of uptake by national

TB programs in resource-limited settings [9]. In Tanzania, the National TB and Leprosy Program does not provide direct guidance on how to screen for diabetes among TB patients [10]. Few studies from Tanzania have been performed to guide the best practice for diabetes screening and to determine which subsets of TB patients may be at highest risk [11,12]. Furthermore, there is emerging evidence that hyperglycemia at levels in the prediabetes range also can increase the risk of developing active TB [13].

Kibong'oto Infectious Diseases Hospital (KIDH) is a regional referral hospital for TB cases from northern Tanzania, and is the national referral hospital for multidrug-resistant (MDR)-TB. We therefore sought to perform glycated hemoglobin (HgbA1c) testing among all patients admitted to KIDH to determine the point prevalence of diabetes (HgbA1c  $\geq$  6.5%) and prediabetes (HgbA1c 5.7%–6.4%) [14,15], and

compare findings among patients with newly diagnosed TB, those admitted for retreatment of TB, and those with MDR-TB.

## Methodology

A hospital-wide cross-sectional initiative was conducted at KIDH during one week in 2014, launched on World TB Day, with the aim to screen all admitted patients. KIDH has a typical inpatient census of 150 TB cases, including MDR-TB patients. General TB wards are segregated by gender but also by those admitted for retreatment. A retreatment case is defined as a patient who is being treated with a retreatment WHO Category II regimen after having failed a prior drug-susceptible TB treatment course, who relapsed after having completed treatment within 18 months, or who defaulted treatment and remains sputum smear positive. Patients on the MDR-TB ward are treated with second-line medications (WHO Category IV) and are increasingly referred from all regions of the country [16]. Hospital chart reviews were performed for basic patient demographics including HIV status and antiretroviral (ARV) use, and sputum smear status on admission (for pulmonary TB patients). Prior diabetes diagnosis was assessed by chart review and patient recall. Height (centimeters) and weight (kilograms) were measured for calculation of body mass index (BMI).

HgbA1c measurement was performed with the point-of-care DCA System Analyzer (Seimens, Washington, USA). Validation was performed with control samples. The patient's finger was cleaned with alcohol and dried with sterile swab prior to being pricked for blood application (1  $\mu$ L) to the system's cartridge. Samples were analyzed within five minutes. HgbA1c values were stratified by American Diabetes Association's recommendations for normal, prediabetes, and diabetes [15].

The hospital initiative was designed and undertaken by the KIDH administration, and approval for analysis of the initiative was additionally granted by the

**Table 1.** Patient characteristics from screening initiative (n = 148).

Characteristic	Result
Age, mean years $\pm$ SD	40.0 $\pm$ 13.5
Gender	
Female	41 (28%)
Male	107 (72%)
Smear status	
Negative	24 (16%)
Scanty	9 (6%)
1+	30 (20%)
2+	38 (26%)
3+	35 (24%)
Extrapulmonary	7 (5%)
Not available	5 (3%)
Body mass index*, mean $\pm$ SD	20.6 $\pm$ 3.6
HIV infected	40 (27%)
Known history of diabetes	
No	145 (98%)
Yes	3 (2%)

\*Calculable in 129 subjects

institutional review boards of Tumaini University, Tanzania and the University of Virginia, USA.

## Results

A total of 148 patients were screened, accounting for all (100%) of the admitted patients during one week. Reflective of usual hospital demographics, the majority of patients were male (72%), and the mean age was 40.0  $\pm$  13.5 years (Table 1). Of those with pulmonary TB and available smear results, 112 (82%) were positive. A narrow range of BMI was noted, mean 20.6  $\pm$  3.6%. Only 3 patients (2%) had a known history of diabetes.

A total of 144 (97%) of patients had HgbA1c results, as very low hemoglobin limited processing in 4 patients. Of the 141 patients without a prior diabetes diagnosis, 3 new diabetes cases were found, yielding a NNS of 47 to diagnose 1 new case of diabetes (Table 2). However, no retreatment case was a known diabetic, therefore the NNS among retreatment cases dropped to 11. The mean HgbA1c among diabetics was 9.5  $\pm$  3.4 percent.

**Table 2.** Hemoglobin A1c distribution among different treatment categories.

	Total (n = 144)*	New (n = 59)	Retreatment (n = 22)	MDR (n = 63)
Normal, HgbA1c $\leq$ 5.6	110 (77%)	46 (78%)	11 (50%)	53 (84%)
Prediabetes, HgbA1 c $\geq$ 5.7 < 6.5	28 (19%)	11 (19%)	9 (41%)	8 (13%)
Diabetes, HgbA1c $\geq$ 6.5	6 (4%)	2 (3%)	2 (9%)	2 (3%)
Univariate odds ratio and 95% CI for risk of prediabetes or diabetes	n/a	Referent	3.2 (1.2–9.0) p = 0.02	0.67 (0.27–1.7) p = 0.39

\*Four patients did not have HgbA1c percent determined (low hemoglobin or otherwise unable to process). Definitions of HgbA1c percent from [14]; MDR: patients admitted for treatment of multidrug-resistant tuberculosis.

**Table 3.** Age and body mass index (BMI) differences stratified by HgbA1c value.

	<b>Normal (n = 59), HgbA1c ≤ 5.6</b>	<b>Prediabetes (n = 22), HgbA1c ≥ 5.7 &lt; 6.5</b>	<b>Diabetes (n = 63), HgbA1c ≥ 6.5</b>
BMI%, mean ± SD	19.6 ± 3.3	21.9 ± 3.0 p = 0.05	25.8 ± 4.9 p = 0.01
Age, mean ± SD	38.9 ± 14.6	41.9 ± 8.8 p = 0.53	49.5 ± 8.1 p = 0.12

One-way ANOVA with between group difference of  $p < 0.001$  for mean BMI and  $p = 0.13$  for mean age. P values in columns reflect Dunnett test comparing mean differences using patients with normal HgbA1c range as a control group.

A stepwise increase of BMI was observed between patients with normal HgbA1c and pre-diabetes, BMI increase of  $2.3 \pm 0.74$  ( $p = 0.05$ ), and between those with normal HgbA1c and diabetes,  $6.2 \pm 1.69$  ( $p = 0.01$ ) (Table 3). A similar non-significant trend was observed for age, but not for other demographic characteristics. Indeed, HIV infection among both diabetics (17%) and pre-diabetics (18%) was less common than in those with normal HgbA1c values (29%). Furthermore, 32 HIV-infected patients were on ARVs, yet only one patient with either pre-diabetes or diabetes had been on ARVs for more than six months, and no patient was on a protease-inhibitor or a nucleotide reverse transcriptase inhibitor known to increase the risk of insulin resistance (*e.g.*, didanosine or stavudine). Importantly however, comparing subjects with  $A1c \geq 5.7\%$  (prediabetes or diabetes) to those with normal A1c levels, and using new TB patients as the referent, retreatment patients were significantly more likely have a  $A1c \geq 5.7\%$  (odds ratio: 3.2, 95% CI: 1.2–9.0;  $p = 0.02$ ), which was not the case for MDR-TB patients (odds ratio: 0.67, 95% CI: 0.27–1.7;  $p = 0.39$ ).

**Discussion**

This hospital-wide cross-sectional analysis of diabetes screening by HgbA1c among TB patients found a NNS of 47 to diagnose one new case of diabetes. Expectedly, diabetes and pre-diabetes was more common in patients of older age and increased BMI. However, half of all retreatment patients had prediabetes or diabetes, which was not the case for patients admitted with an initial episode of TB or MDR-TB. The diabetes co-prevalence among our population contrasts with the far higher proportions found by HgbA1c screening in studies from Southeast Asia, where the community burden of diabetes is greater [8,17], but demonstrates the importance of performing such local investigation before adopting a widespread policy.

Given the association of the diabetic disease state with poor treatment outcomes [3-6], there is biological plausibility for our finding of worse glycemic control in patients with recent TB treatment failure or relapse.

Whether this association may be secondary to poor host immunological response to TB infection or, as has been found in other settings, that diabetes/TB patients have suboptimal circulating anti-TB medications that could have predisposed to treatment failure [6], we believe retreatment patients represent a high-yield subpopulation for screening. KIDH administration now plans to screen all retreatment patients prospectively to determine if this association is maintained.

Few comparative studies of this kind have been performed in Tanzania. In a 1990 study at a large urban teaching hospital among exclusively smear-positive pulmonary TB patients [11], patients were screened by oral glucose tolerance testing (OGTT) and the overall prevalence of diabetes was 4%, which did not markedly differ from our findings. A recent case-control study using pulmonary TB cases at a referral hospital found a prevalence of diabetes of 16.7% compared to 9.4% among non-TB neighborhood controls, but testing was also performed by OGTT and fasting blood glucose [12]. The WHO and other advisory bodies recommend HgbA1c, fasting blood glucose, or OGTT as equivalent means for screening [14,15], but we favor the point-of-care HgbA1c method, given the ease of administration in our setting and the clinically actionable snapshot of glycemic control over the patient’s prior three months. For example, even among the known cases of diabetes, only one was at target  $HgbA1c < 7\%$ , while the other patients had markedly uncontrolled values of 13.1% and 14.0%. In our resource-limited setting, such measurement allows more informed long-term individualization of oral hypoglycemic and insulin-based therapy.

**Conclusions**

Despite the limitations inherent in a point-prevalence design, we believe this type of initiative allows for a resource-conscious deployment of diabetes screening informed by local epidemiology. Prospective study among high-risk populations such as those being admitted for retreatment, patients with higher BMI or age, or overt symptoms of diabetes will further refine our hospital’s approach. We recommend in other

settings where our findings could be generalizable, for instance in East Africa, that similar local screening initiatives be pursued. Bidirectional screening for TB in diabetes clinic patients, for instance, may also be worthwhile, given the prospective relationship of incident TB and diabetic disease severity found earlier in Tanzania [18] and the advent of more sensitive TB diagnostics [7], but it must first be informed by an operational approach, as was completed for this work.

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