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New screening technologies for type 2 diabetes mellitus appropriate for use in tuberculosis patients

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Type 2 diabetes mellitus (DM), which is epidemic in low- and middle-income countries (LMICs), may threaten gains made in tuberculosis (TB) control, as DM is both a major risk factor for developing active TB and it can lead to adverse TB treatment outcomes. Despite World Health Organization guidance that all TB patients should be screened for DM, most facilities in LMICs that manage TB patients do not currently perform screening for DM, due in part to the cost and complexity involved. DM screening is further complicated by the presentation of transient hyperglycemia in many TB patients, as well as differences in diabetes risk factors (e.g., body mass index) between TB patients and the general public. In this article, we review existing and new technologies for DM screening that may be more suitable for TB patients in LMICs. Such methods should be rapid, they should not require fasting, and they should allow the provider to differentiate between transient and longer-term hyperglycemia, using inexpensive tools that require little training and no specialized infrastructure. Several methods that are currently under development, such as point-of-care glycated hemoglobin and glycated albumin assays, non-invasive advanced glycation end-product readers, and sudomotor function-based screening devices, offer interesting performance characteristics and warrant evaluation in populations with TB.

Type 2 diabetes mellitus (DM) triples the risk of developing tuberculosis (TB), and rates of TB are higher in people with DM than in the general population.[1,2] DM is also associated with adverse TB treatment outcomes.[2] With the epidemiological transition underway in many countries around the world, current predictions indicate that the prevalence of DM will reach 552 million by 2030.[3] Approximately 80% of these cases will be in low- and middle-income countries (LMICs), where TB prevalence is high.[4] Although the links between diabetes and TB have been known for decades,[5,6] the unprecedented global rise in DM led the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease to issue a global recommendation in 2011 that all TB patients should be screened for DM and vice versa,[4] and countries including China and India have commenced TB-DM screening programs.[7–9] Despite this, global response to the crisis has been hampered by a lack of knowledge regarding the most appropriate screening methods and technologies to use in TB settings.[4] The need to develop and evaluate more accurate, rapid, non-invasive and cost-effective point-of-care (POC) diagnostic and monitoring tests—including measurements of blood glucose and blood glycated hemoglobin (A1c)—was acknowledged in 2011 at a consultation meeting of global experts on TB and DM.[10]

Technologies for the detection of diabetes face special challenges in their use among TB patients.[9] As with other infectious diseases, TB may temporarily elevate blood glucose levels, resulting in false-positive DM diagnoses.[9,11] Current DM detection tools are not optimized for LMICs, where the majority of TB patients are found,[4] and are often inaccurate, expensive, invasive and inconvenient.[12] Multiple tests are often required to establish a diagnosis, as is referral to a specialist center for confirmatory diagnosis.[13] These circumstances present special challenges for TB patients who are already burdened with the financial costs associated with 6–24 months of TB treatment, depending on whether drug resistance is present or not. A systematic review found that the costs (both direct and indirect) associated with TB treatment in sub-Saharan Africa can be as much as 10 times the average annual income for TB patients in the poorest 20% of the population, and for many households such costs are considered catastrophic.[14]

Nonetheless, screening and treatment for hyperglycemia and DM is essential, due to the potential impact on TB treatment outcomes and the effectiveness of TB medications.[15,16] Individuals with elevated blood glucose may have delayed or impaired recovery, face worse treatment outcomes, or may even require altered doses or schedules of TB medications.[15,16]

This article builds on the recent publication from Weigl and Drake in *Point of Care*,[12] and will outline a proposed target product profile for a POC DM test for use in TB patients. Optimal test characteristics, including accuracy, suitability for use in current TB program structures, patient acceptability, suitability for use given TB patient infection status, convenience and cost will be considered. The current pipeline for POC DM screening technologies appropriate for LMICs will then be examined to identify the candidate technologies that best meet the optimal test characteristics as described, and which may require further evaluation within TB populations.

Existing technologies and approaches for diabetes screening in tuberculosis patients

According to the WHO, DM is diagnosed by the presence of one of the following:[17] a fasting plasma glucose

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level ⩾ 7.0 mmol/l (126 mg/dl); plasma glucose ⩾ 11.1 mmol/l (200 mg/dl) 2 h after a 75 g oral glucose load in a glucose tolerance test; symptoms of hyperglycemia and casual plasma glucose ⩾ 11.1 mmol/l (200 mg/dl); glycated hemoglobin (HbA1c) ⩾ 6.5%.[18] A clinical DM diagnosis also requires retesting on another day by any of the above methods, unless the patient is symptomatic and the plasma glucose is unequivocally elevated.[18] It is important to note the overlap between DM screening and diagnosis, as various screening and diagnosis algorithms may be employed.[19] The WHO recommends screening TB patients for DM using existing DM country guidelines.[4] Table 1 shows DM screening and diagnosis guidelines from a selection of the 22 countries with the highest TB burdens in the world from which information regarding national DM guidelines was available. [20–27]

Screening approaches for DM in TB patients—as in the general population—may include questionnaire-based risk assessments (used to create risk scores) as well as blood, urine, and non-invasive tests that determine the levels of biochemical markers or physiological responses correlated with diabetes risk.[19,28]

Diabetes risk assessments

DM risk assessment questionnaires commonly include the following components: age; sex; family history; biometric measurements such as body mass index (BMI), waist circumference, and waist-to-hip ratio; and history of hypertension.[19,28] Risk of DM is generated through a scoring system related to each of these attributes, and a biochemical test may be included automatically, or a high score may lead to a biochemical test.[19, 28] The benefits of using DM risk scores to evaluate DM risk in TB patients in the context of TB programs include the fact that they are relatively easy to administer (TB program staff could potentially be trained relatively easily to administer a DM risk score), promote recommended guidelines relating to targeted biochemical screening, and are low cost in themselves.[28] One disadvantage associated with using DM risk scores in the context of TB programs is the fact that, of the seven risk scores recommended for adaptation in routine clinical practice,[29] all were developed in North America or Europe, and none of the 22 countries that account for 90% of the global TB burden is in Europe or North America.[30] This raises questions regarding the applicability of the risk scores in these countries. In addition, not enough is known about how active TB disease influences the phenotypic characteristics associated with DM as measured by standard risk scores; for example, TB-DM co-morbid patients may have, on average, a lower BMI or lower hip-to-waist ratio than their TB-negative DM patient counterparts. This article proposes that more research is required to develop a risk score optimized for use in TB populations.

Biochemical tests

The most commonly used biochemical diabetes screening and diagnostic tests are blood or plasma glucose tests, variants of which include random plasma glucose (RPG), random blood glucose, fasting plasma glucose (FPG), fasting blood glucose (FBG) and the oral glucose tolerance (OGTT) and challenge tests.[17] Glucose

TABLE 1 DM screening and diagnosis guidelines from selected high TB burden countries[20–27]

Country	DM screening	DM diagnostic criteria
Bangladesh[20]	Venous RPG	At least two of: More than one characteristic and sign of DM Venous FPG >7.0 mmol/l
	Urine glucose	Venous RPG taken at least 2 h after eating or after taking 75 g glucose ⩾11.1 mmol/l Presence of diabetic retinopathy, or Random sample on more than one occasion >11.1 mmol/l
Brazil[21]	Risk score Capillary glucose test	FBG >126 mg/dl, and 2 h after ingestion of 75 g anhydrous glucose, ⩾200 mg/dl + symptoms FBG ⩾126 mg/dl on more than one occasion FBG >126 mg/dl + symptoms
China[22]	RBG	FBG ⩾7.0 mmol/l on at least two occasions
Ethiopia[23]	Capillary glucose test	At least two of the following on subsequent days: FBG ⩾126 mg/dl RBG ⩾200 mg/dl 2 h oral glucose test ⩾200 mg/dl, as confirmed on a subsequent day by any one of the three methods
India[24]	Capillary glucose test, random	2 h post-glucose load ⩾200 mg/dl
	Risk score	FBG ⩾ 126 mg/dl
Kenya[25]	Capillary glucose test	Venous FPG >7.8 mmol/l on more than one occasion Plasma glucose >11.1 mmol/l in symptomatic patients
South Africa[26]	Risk score	In patients without symptoms, at least two of the following:
	FPG	FPG ⩾7.0 mmol/l 2 h plasma glucose ⩾11.1 mmol/l
	RPG	RPG ⩾11.1 mmol/l
	A1c	A1c >6.5% One of the above + symptoms
Uganda[27]	Risk score Urine glucose	Blood glucose
	Blood glucose A1c	A1c

DM = diabetes mellitus; TB = tuberculosis; RPG = random plasma glucose; FBG = fasting blood glucose; RBG = random blood glucose; FPG = fasting plasma glucose; A1c = blood glycated hemoglobin.

testing may be conducted via venous blood usually drawn for laboratory instrument-based testing, or via capillary blood—or fingerprick—for glucometer testing using portable POC devices. FPG and RPG are single-point glucose measurements taken in blood after fasting or at random times, respectively, whereas the OGTT measures the response to a glucose challenge by measuring blood glucose levels before and after receiving it (the first glucose measurement being an FPG).[28] The OGTT is considered the gold standard diagnostic test for DM,[17] although its inconvenience (patients must wait for 2 h) and cost makes FPG preferable in clinical practice settings.[12,28] Other common tests include urine glucose and A1c measurements.[19] Although the WHO has advised that A1c can also be considered a diagnostic test for DM, in addition to its use as a glycemic control monitoring test for diagnosed DM patients,[31] of the countries listed in Table 1, only South Africa and Uganda use it for either purpose. The usefulness of urinary glucose as a screening test for undiagnosed DM is limited because of its low sensitivity, which some studies show to range from 21% to 64%, although specificity is high, at >98%.[19]

There are notable disadvantages with each of these currently used and recommended tests in relation to the TB care context. FPG and OGTT both require patient preparation in the form of fasting, and in the case of OGTT, extended clinic waiting times and multiple blood draws are required.[12,32] These approaches therefore reduce the ability to test TB patients opportunistically as they come into contact with the health system, thus delaying diagnosis and resulting in increased risk of serious consequences, as TB patients with DM are more likely to experience delays in sputum culture conversion, increased case fatality rates during treatment, and increased relapse rates of TB after successful completion of treatment.[2,33] In many of the countries listed in Table 1, DM screening is performed via FPG or RPG, using a POC glucometer device on a capillary specimen. The WHO has recognized the widespread use of capillary sampling in LMICs, although venous plasma glucose is considered the standard measurement and reporting method.[18] Although venous and capillary measurements give the same fasting result, unfortunately the most cost-effective and commonly used glucometer devices exhibit universally low accuracy, often due to incorrect and/or infrequent calibration.[34] Moreover, although it has a specificity of >90%, the sensitivity of FPG is only 40–65%.[32] RPG does not require fasting and is therefore more conducive to opportunistic screening of TB patients, but as with FPG, POC glucometer devices are commonly used. In the case of RPG, capillary glucose samples give values that are higher than venous sample values, and therefore value conversion must be performed.[18] This complication is in addition to the poor and variable sensitivity and specificity of RPG of respectively 40–79% and 66–96%.[32]

A1c has advantages over both FPG and RPG in that the test does not require fasting and is generally more sensitive than FPG, at 78–81% sensitivity, although its specificity is 79–84%.[32] A1c is especially sensitive in the detection of early type 2 DM in at-risk subjects.[35] The main drawbacks in the use of A1c for TB patients are the lack of standardization and the cost; the consumables required for POC-compatible A1c instruments, and the instruments themselves, are cost-prohibitive in many LMICs.[12] In addition, race, ethnicity and hemoglobin variants may all impact on A1c readings, as is the case with conditions such as anemia (including that caused by malaria) and vitamin B12 deficiency.[36,37] Taking these factors into consideration, there is a paucity of data regarding A1c performance from the high TB burden countries featured in Table 1. Despite the low sensitivity of urinary glucose testing, it may be useful in LMICs where no other procedure is possible.[19] Because of the importance of high sensitivity in a DM screening test for TB patients, however, urinary glucose testing is considered to have serious limitations.

The transitory hyperglycemia that many TB patients exhibit due to the nature of the disease often resolves upon commencement of TB treatment.[4] To this end, to accurately represent true DM presence or risk, a DM screening test for TB patients should represent a deviation of actual blood glucose from normal values averaged over a time period long enough to distinguish between temporary elevation in blood glucose brought on by active TB. The biochemical tests commonly used in the high TB burden countries shown in Table 1 face disadvantages in this regard. FPG and RPG are single-point glucose measurements and are therefore unable to identify chronically elevated blood glucose, and OGTT measures the response to a glucose challenge.[12] Of the commonly available tests, A1c is the most appropriate for identifying chronic hyperglycemia, as it represents blood glucose levels averaged over 3 months,[36] although as discussed, the test is cost-prohibitive for many LMICs.[12]

Table 2 reviews key attributes and performance of these various tests for DM screening and diagnosis.[17,35,38] The selection of a screening tool can be limited by cost, complexity of use and a lack of trained personnel, and, in some cases, a lack of availability.

TABLE 2 Common DM screening and diagnostic tests[17,35,38]

Test	FPG, FBG	OGTT	RPG, RBG	Urine	A1c
Measures	Glucose post 8 h fast	Glucose after fasting + 2 h post-glucose load	Glucose regardless of when person last ate	Presence of glucose in urine	% of Hb that is glycated
Specimen	Capillary venous blood	Capillary venous blood	Capillary venous blood	Voided mid-stream urine	Capillary venous blood
Test	Glucometer laboratory measurement	Glucometer laboratory measurement	Glucometer laboratory measurement	Dipstick	Glucometer laboratory measurement
Performance	40–65% sensitivity, >90% specificity[17]	96.8% max sensitivity, 90.8% max specificity[38]	40–79% sensitivity, 66–96% specificity[17]	21–64% sensitivity; specificity >98%[17]	78–81% sensitivity, 79–84% specificity[35]
Normal range	FPG ⩽99 mg/dl (7.0 mmol/l)	2 h PGL ⩽139 mg/dl (7.0 mmol/l)	RPG <200 mg/dl (11/1 mmol/l)	0–15 mg/dl	A1c <5.7%
Pre-diabetes	FPG = 100–125 mg/dl (5.6–6.9 mmol/l); IFG	140–199 mg/dl (7.8–11.0 mmol/l); IFG	Cannot be used to diagnose pre-diabetes	>15 mg/dl	A1c = 5.7–6.4%.
Distinguishes transient hyperglycaemia	No	No	No	No	Yes

DM = diabetes mellitus; FPG = fasting plasma glucose; FBG = fasting blood glucose; OGTT = oral glucose tolerance test; RPG = random plasma glucose; RBG = random blood glucose; A1c = blood glycated hemoglobin; PGL = post-glucose load; IFG = impaired fasting glucose.

Typically the urine glucose test strips are the least expensive, while the hemoglobin A1c tests are the most expensive screening option.[39]

Tuberculosis program requirements

TB patients in the public sector are usually diagnosed and managed via two mechanisms: 1) through a vertical TB program structure, via TB clinics and microscopy centers/laboratories staffed by specialized personnel, as is the case in India,[40] a country that accounted for 26% of global TB cases in 2011,[30] or 2) in an integrated manner, where TB is one of numerous conditions managed as part of a package of primary health care interventions overseen by multidisciplinary staff within one facility, as in Mexico.[41] Often a combination of the two systems is present, in that the TB clinic and microscopy center/laboratory are physically co-located within the primary health care structure, and staff are shared between the two, as in Tanzania.[42] To reduce the burden of referral on TB patients (even within the same structure), an optimal screening test is one that can be used safely and with acceptance by the cadres of clinical and laboratory staff who currently manage TB patients, integrated within their current systems and using existing infrastructure, such as ambient temperature storage and adequate waste disposal for portable glucometer test strips. A recent study highlighted that a waste management system in TB microscopy centers existed in only 50% of the 22 high-burden TB countries.[43] The indoor temperature always remained below 35°C in only 23% of the countries, but 82% had gloves in stock.[43]

The DM burden in the 22 high-burden TB countries continues to grow,[3] and it is estimated that globally between 30% and 90% of those with DM are undiagnosed.[28] In examining the various disadvantages associated with current DM screening tests relating to their use in TB patients, it is clear that to address the WHO's recommendation for the universal screening of TB patients for DM, two distinct screening needs emerge: 1) a POC DM assay that requires no patient preparation, is acceptably accurate, sensitive and specific, is low cost, requires minimal infrastructure and is easy to use; and 2) an assay that differentiates transient hyperglycemia from pre-diabetes and DM.

TARGET PRODUCT PROFILE FOR A DIABETES POINT-OF-CARE SCREENING TEST FOR TUBERCULOSIS PATIENTS

A target product profile (TPP) is simply a statement of the essential attributes of a clinically and commercially successful product; many TPPs, however, are not widely publicized,[44] despite the fact that they can be very valuable in terms of evaluating the appropriateness of existing technologies, and in guiding discovery and development activities.[45] A TPP can stimulate innovation and development by reducing the risks for companies that are considering developing products for underserved markets such as those found in many high-burden TB countries, by providing a consensus document containing optimal target product specifications developed by experts and informed by clinical needs assessments.[44,45]

In identifying a TPP for a DM POC screening test for TB patients, there is significant overlap with potential TPPs for general populations in LMIC settings. Indeed, the TPP proposed here builds upon the TPP for a DM POC screening test for low-resource settings described by Weigl and Drake.[12] Although there are overlaps, there is utility in identifying the attributes of a DM screening test that can be easily deployed within TB program structures, poses minimal burden upon TB patients, and is appropriate given the physiological attributes of this population. Appropriate tests should be able to be deployed within optimized algorithms that may include non-device-based screening approaches, and algorithm research and development should be prioritized in this regard. This article proposes the following ideal attributes for a DM POC screening test for use in TB patients:

- *Ability to distinguish between short-, medium- and longer-term glycemic control with a single measurement at a single point in time.* To avoid false-positive results, determining multiple parameters correlated to chronic hyperglycemia is especially important in TB patients, as active TB can result in transient hyperglycemia.[7] Such a test would be useful not only for screening but also for glycemic control monitoring in patients already identified as having prediabetes or DM.
- *Low cost.* A benchmark cost for comparison would be US$1, which is comparable to that of the glucose test strips used for RPG, FPG, or OGTT tests.[12] Cost will be a critical consideration in the operationalization of the WHO's recommendation to screen all TB patients for DM, and resource-poor TB programs and nascent, underfunded non-communicable disease programs will have to work together to identify additional budgetary allocations for screening and ongoing care and management of TB-DM patients.
- *Ability to be administered without fasting.* Ideally, there should be no preparation required for the patient, to avoid the need for repeat visits. Fasting may present an additional burden for TB patients in particular, who already face significant loss of income and inconvenience due to the repeated interactions with the health system required by 6–24 months of treatment.
- *Minimal waiting time for results.* The presence of DM increases the risk of poor treatment outcomes in TB patients.[2] It is therefore imperative that DM in TB patients be identified and managed without delay.
- *High sensitivity.* Although a screening test/device should ideally have as high a sensitivity and specificity as possible, trade-offs always have to be made with respect to test function and sensitivity and specificity. A screening tool should primarily serve a 'rule-out' function, and have as high a sensitivity as possible to ensure that patients are not mistakenly declared negative,[46] and, in the case of a TB patient, falsely determined to be DM-negative, risking adverse treatment outcomes.
- *Simplicity of use.* The reality of many settings is that the management of TB patients is left to lower cadres of health workers. To reduce the burden of referral on TB patients, an optimal DM screening device should be simple enough for use by the health care and laboratory staff currently providing care to TB patients.
- *Non-invasive/minimally invasive.* The priority for any screening device should be to minimize patient inconvenience and discomfort by requiring only non-invasive or minimally invasive sample collection.
- *Minimal requirement for associated infrastructure.* Given the infrastructure constraints experienced by TB microscopy centers in the 22 high-burden TB countries,[43] an ideal test/device would require no maintenance or calibration, and would have no temperature or storage control requirements. There should not be any need for reagents that are not included with the disposable or kit.
- *Indigenous manufacture and distribution.* Distribution and marketing costs for glucose tests can comprise more than 50% of the total end-user costs.[12] Any optimal test/device should be able to be manufactured in high TB burden countries and distributed using existing supply chains, to keep costs to a minimum. The cost savings associated with producing a DM test close to or within a target country can have a huge impact.

DIABETES SCREENING TECHNOLOGY PIPELINE—ARE THERE CANDIDATES SUITABLE FOR TUBERCULOSIS PATIENTS?

The pipeline for DM detection technologies is relatively robust, although product development priorities have been shaped by the traditional markets in high-income settings.[12] This has meant that many promising candidate technologies are not fully optimized for use in LMIC settings such as those in Table 1. An extensive review of the literature has shown no previous studies that have examined the attributes of technologies currently in the pipeline for applicability in TB programs, given the particular characteristics required. Among the promising novel DM screening technologies currently under investigation and development, some are in routine use, but none has been widely evaluated for use in TB patient populations. Table 3 provides a summary of novel DM screening technologies identified, and indicates whether they meet the proposed TPP requirements described earlier.[35,47–49] A summary of each category of test is also provided below.

Point-of-care compatible A1c readers and low-cost test disposables

A1c readers are one of a class of DM screening devices that determine glucose in protein-bound form. Glucose not only exists in free forms, it also persists in protein-bound forms in blood and other tissues (e.g., glycated hemoglobin and glycated albumin in blood, and advanced glycation end products in skin). After the initial formation of a Schiff base by glucose and protein molecules, an irreversible reaction forms a stable ketoamine. As the reaction is irreversible, in vivo protein half-life determines the averaging time of glycemic control. Although A1c readers are now POC-compatible, accurate and provide blood glucose levels averaged over a 3-month period, their suitability for use in TB programs is limited by the fact that they are invasive (requiring a finger-prick sample) and require expensive disposables that require refrigeration. Low-cost A1c test disposables are required.[12]

Autofluorescence-based readers

This category of device measures skin fluorescence due to the accumulation of DM-related advanced glycation end products (AGEs) in the dermal collagen, and biomarkers of metabolism and oxidative stress to determine a subject's risk of having undiagnosed pre-diabetes and DM.[50] AGEs are thought to play a central role in the pathogenesis of DM complications, and are the result of a chain of chemical reactions after an initial glycation reaction.[50,51] Specific and accurate measurement of AGEs requires gradient high-pressure liquid chromatography analysis or gas or liquid chromatography-mass spectrometry, which is not available in most clinical settings.[51] For this reason, non-invasive tools using skin autofluoresence quantification that correlate with levels of tissue AGEs have been developed that take advantage of the characteristic fluorescence of AGEs in the skin.[49] Due to the fact that the glycated products (the major contribution in fluorescence comes from fluorescent AGEs linked mostly to collagen, but also to other proteins and lipids) remain present in the dermal layer for a long period of time, measurements from AGE readers represent averages of hyperglycemia over a long period of time (average 12 months);[51] they therefore present an opportunity for use in TB patients, given the need to distinguish medium- and long-term glycemic control from short-term, infection-induced hyperglycemia.

Two non-invasive AGE devices are currently at an advanced stage of development, by the companies DiagnOptics Technologies BV (AGE Reader™; Groningen, The Netherlands) and Veralight (SCOUT DS®; Miraculins Inc., Winnipeg, MB, Canada).[12] While the capital cost of their devices is currently quite high, they are simple to use, and there are no consumables and little to no maintenance, although electricity is required. They do not require patient fasting or preparation and are non-invasive, and both provide results in a few short minutes after the patient places the underside of the forearm on the device.[12] Although more studies are required, one study demonstrated the SCOUT DS® to have 74.7% sensitivity, and the same study calculated the sensitivity differential to mean that the device would detect 28.8% more individuals in the OGTT-defined positive screening class than FPG testing and 17.1% more than A1c testing.[49] Despite these promising results, more information is needed regarding the performance of AGE readers in the 22 high TB burden countries, given potential variations in performance due to genetic and socio-cultural variations, skin color, skin dryness, or the use of topical creams and substances. Overall, in addition to their non-invasiveness and operational advantages, AGE readers offer the potential for very low-cost screening. They do not require disposables, are easy to operate by minimally trained users, and have relatively low operating costs. The initial instrument costs could be amortized very quickly in settings with high-patient throughput, and with sufficiently high volumes per test, costs might ultimately be much lower than A1c per-test costs.

TABLE 3 Novel DM screening methods with potential utility in TB populations[35,47–49]

	1,5-anhydroglucitol	Glycated albumin and fructosamine	Sudomotor function readers	POC A1c readers	AGE readers
Distinguishes transient hyperglycemia	1–3 months	GA = 1 month F = mixed	Yes	3 months	12 months
Low cost	No	Yes	Low per test cost, high device cost	Low device cost, high per test cost	Low per test cost, high device cost
No fasting	Yes	Yes	Yes	Yes	Yes
<5 min results	No	Yes	Yes	Yes	Yes
High sensitivity	Yes	64.1%[47]	75%[48]	78–81%[35]	74.7%[49]
Simple use	No	No	Yes	Yes	Yes
Non-invasive	No	No	Yes	No	Yes
No calibration	No	No	Yes	No	Yes
No minimum operating temperature	Yes	No	No	No	No
POC	No	Yes	Yes	Yes	Yes
Other	Early in development pipeline	Early in development pipeline	Early in development pipeline		Early in development pipeline

DM = diabetes mellitus; TB = tuberculosis; POC = point-of-care; A1c = blood glycated hemoglobin; AGE = advanced glycation end product; GA = glycated albumin; F = fructosamine.

Sudomotor function devices

The EZSCAN Sudomotor reader (Impeto Medical, Paris, France) is an alternative DM screening device based on electrochemical potential measurements across hand and foot skin surfaces to determine emergent neuropathy.[52] Small fiber neuropathies are common in people with insulin resistance and prediabetes.[48] EZSCAN is a dynamic test equivalent to a stress test, which measures the capacity of the sweat glands to release chloride ions in response to electrochemical activation.[48] A low voltage of variable amplitude is applied to electrodes on the skin in regions with a high density of sweat glands (palms, feet), and the electrical potential difference caused by the electrochemical reaction on these electrodes is measured.[48] The information is then used to determine the patient's cardiometabolic risk.[53] The test does not require patient preparation, such as fasting, and does not require blood drawing. Results are available within 2 min, and clinical studies have shown their sensitivity and specificity to be as high as 75% and 100%, respectively.[48,53] More studies are required to assess the utility of the test for TB patients.

Other promising biomarkers

The ability to distinguish between short-, medium- and longer-term glycemic control with a single measurement at a single point in time is a key priority for any DM screening device intended for use in TB populations. To this end, a possible solution may be the development of a multivalent platform that contains a set of analytical targets from glycated products selected to demonstrate a range of half-lives, allowing the differentiation between short-, medium- and long-term glycemic control. Promising biomarkers are currently being evaluated, for example, that identify physiological changes due to elevated glucose levels early in pregnancy, which result in transitory hyperglycemia.[12] The main biomarker being investigated in this regard is glycated albumin (GA), which remains in circulation approximately one third as long as A1c; a GA reading will thus represent the effects of elevated glucose over an average of 1 month. [54]

GA is currently being investigated by PATH in relation to a gestational DM project, in addition to fructosamine and 1,5-anhydroglucitol (1,5-AG).[12] Fructosamine measures a mixture of glycated proteins that exhibit both longer and shorter half-lives than GA, and 1.5-AG has a very short half-life, averaging glycemic control for a 1–3 month period.[55] Other markers that have thus far mainly been investigated in relation to gestational DM, but may have utility for DM screening in TB patients, include cytokines, chemokines, hormones and transcription factors stimulated by the AGE/receptor for advanced glycation end-product signaling pathway.[56]

The benefits of a multivalent diagnostic platform are many, and additional parameters of relevance to TB patients, such as the human immunodeficiency virus, could be tested on such a screening platform.

CONCLUSION

With an estimated 8.7 million new cases of TB in 2011, and the majority of these in LMICs,[30] the ability to implement the WHO's recommendation that all TB patients be screened for DM will require the identification of technologies that are appropriate for TB patients and current TB program structures. Research and advocacy are necessary to ensure that evidence is generated regarding the potential for the DM technologies currently in the pipeline to be used in TB populations, given current program structures. This article provides a first step towards understanding the current landscape of DM screening technologies and an analysis of the opportunities and challenges associated with each. It is important to note, however, that while better screening tools can improve and increase the diagnosis of DM among TB patients, TB patients must also have access to treatment, monitoring and ongoing care for DM and support to successfully complete their TB treatment.

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L'épidémie de diabète sucré (DM) de type 2 dans les pays à revenus faibles et moyens (LMIC) peut constituer une menace pour les progrès de la lutte contre la tuberculose (TB), car le DM est à la fois un facteur majeur de risque et de développement d'une TB active et peut aussi entrainer des résultats défavorables du traitement de la TB. En dépit de la directive de l'Organisation mondiale de la Santé selon laquelle tous les patients TB devraient faire l'objet d'un dépistage pour le DM, la plupart des services des LMIC qui traitent les patients TB ne réalisent pas actuellement le dépistage du DM, en partie en raison du coût et de la complexité qu'il implique. Le dépistage du DM est par ailleurs compliqué par l'existence d'une hyperglycémie transitoire chez beaucoup de patients TB ainsi que par les différences de facteurs de risque de DM (par exemple l'indice de masse corporelle) entre les patients TB et la population générale. Dans cet article, nous révisons les technologies existantes et nouvelles pour le dépistage du DM qui pourraient être les plus applicables aux patients TB dans les LMIC. De telles méthodes devraient être rapides, elles devraient ne pas exiger le jeûne et elles devraient permettre aux pourvoyeurs de soins de distinguer entre des hyperglycémies transitoires et de plus longue durée au moyen d'outils peu coûteux, n'exigeant que peu de formation et aucune infrastructure spécialisée. Différentes méthodes sont actuellement en cours de développement, tels que les tests sur l'hémoglobine glycosylée aux lieux de soins et sur l'albumine glycosylée, les lecteurs des produits finaux d'une glycation avancée non-invasive et les outils de dépistage basés sur la fonction sudomotrice ; elles offrent des caractéristiques intéressantes de performance et méritent une évaluation dans les populations TB.

La diabetes (DM) de tipo 2 presenta características epidémicas en los países con ingresos bajos e intermedios (LMIC) y puede poner en peligro los avances alcanzados en materia de control de la tuberculosis (TB); la DM constituye un factor de riesgo importante de padecer la enfermedad TB activa y también puede tener consecuencias desfavorables en el desenlace del tratamiento antituberculoso. Pese a la recomendación de la Organización Mundial de la Salud de realizar la detección sistemática de la DM en todos los pacientes TB, la mayoría de los establecimientos que atienden a estos pacientes en los LMIC no cumplen con esta práctica, en parte debido a los costos y a la complejidad de la misma. La detección de la DM se complica además por la hiperglucemia transitoria que suele observarse en muchos pacientes TB y por las diferencias en los factores de riesgo de DM, presentes en los pacientes con TB y la población general, por ejemplo el índice de masa corporal. En el presente artículo se analizan las técnicas existentes y los nuevos métodos de detección sistemática de la

DM que pueden ser más adaptados a los pacientes con TB de los LMIC. Estos métodos deben ser rápidos, no deben precisar el estado de ayuno y deben permitir al profesional de salud diferenciar entre la hiperglucemia transitoria y la hiperglucemia de largo plazo, mediante la utilización instrumentos de bajo costo, que exijan poco entrenamiento y no necesiten infraestructuras especializadas. En la actualidad, se encuentran en curso de desarrollo varios métodos como las pruebas de hemoglobina glucosilada y albúmina glucosilada realizadas en el punto de atención, los lectores no invasivos de productos finales de la glucosilación avanzada y los dispositivos de detección basados en la función sudomotora; estos métodos ofrecen características de rendimiento interesantes y merecen una evaluación en las poblaciones de pacientes con diagnóstico de TB.

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