

Clinical challenges in the co-management of diabetes mellitus and tuberculosis in southern Africa

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Abstract

Over the past 20 years, tuberculosis incidence in southern Africa has increased at an alarming rate, fuelled primarily by the human immunodeficiency virus epidemic. The emerging prevalence of diabetes mellitus in the region represents a new threat to tuberculosis control. The intersecting double burden is a cause for concern since diabetes mellitus increases the risk of tuberculosis and results in poor treatment outcomes. This review article discusses the evidence of a causal association between these two conditions, and examines the numerous clinical challenges that relate to tuberculosis and diabetes mellitus co-management. Diabetes is associated with a more advanced age and body weight in patients with tuberculosis, although not with a specific clinical presentation of tuberculosis. Rifampicin adversely alters glycaemic control by lowering the concentrations of most oral antidiabetic drugs. Poor glycaemic control, possibly exacerbated by tuberculosis and anti-tuberculous therapy, is an important contributing factor to tuberculosis case fatality and relapse. Clinicians need to be aware of these clinical and pharmacological challenges when co-managing these complex diseases.

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Introduction

Over the past 20 years, the tuberculosis incidence in southern Africa has increased at an alarming rate, fuelled primarily by the human immunodeficiency virus (HIV) epidemic. The emerging prevalence of diabetes mellitus in the region represents a new threat to tuberculosis control. In 2011, nearly two-million people in South Africa were living with diabetes mellitus. This number is expected to increase by 30% by the year 2030.¹ Not only does diabetes contribute to a person's risk of developing tuberculosis, but it also makes it more difficult to treat those who have both diseases. The prompt detection of tuberculosis in patients with diabetes and the early recognition of diabetes mellitus in new patients with tuberculosis can improve the clinical outcomes of individuals living with dual diagnoses. In this review, the clinical presentation of tuberculosis in patients with diabetes is discussed, as well as challenges in co-managing these two diseases. Important public health implications of rising diabetes mellitus prevalence in tuberculosis-endemic settings in Africa are considered.

Epidemiology

Studies from middle- and high-income countries have clearly demonstrated that diabetes is associated with

an increased risk of tuberculosis.² A recent systematic review of 13 observational studies found that people with diabetes mellitus had a 3.11 times higher risk of acquiring tuberculosis (95% confidence interval 2.27-4.26) compared to people without diabetes mellitus.³ Furthermore, the analysis demonstrated that young patients with diabetes were at a higher risk of acquiring tuberculosis, and the relative risk was higher in countries with a higher incidence of tuberculosis,³ suggesting that a similar prevalence of diabetes mellitus might contribute to the tuberculosis epidemic in developing countries. Only a few studies have assessed whether or not patients with tuberculosis and diabetes mellitus had type 1 diabetes mellitus or type 2 diabetes mellitus. However, available data from Africa are consistent with research from high-income countries which report that type 2 diabetes mellitus is more prevalent, but type 1 diabetes mellitus is associated with a higher risk of tuberculosis.² Studies from Ethiopia and Tanzania have demonstrated that patients with type 1 diabetes mellitus have a three- to fivefold higher risk of developing tuberculosis than patients with type 2 diabetes mellitus.^{4,5}

In Africa, the biggest driver of the tuberculosis epidemic is HIV. Individuals with HIV are 25 times more likely to develop tuberculosis in sub-Saharan Africa

than HIV-negative individuals in the same setting.⁶ While a paucity of data suggests that diabetes is an important determinant of tuberculosis transmission in southern Africa, one recent study in Tanzania found that the prevalence of diabetes was twice as high in people with tuberculosis compared to the prevalence in people without tuberculosis.⁷

Causal association: diabetes increases the risk of tuberculosis

Considerable evidence demonstrates that diabetes increases susceptibility to *Mycobacterium tuberculosis* infection and the development of tuberculosis. Research in animal models has demonstrated that mice with diabetes who were experimentally infected with *M. tuberculosis* had higher bacterial loads compared to euglycaemic mice, regardless of the route of inoculation.^{8,9} Compared to euglycaemic mice, chronically diabetic mice also had a significantly lower production of interferon-gamma and interleukin-12 and fewer *M. tuberculosis* antigen-responsive T cells early in the course of *M. tuberculosis* infection, marking a diminished T helper 1 adaptive immunity, which plays a role in controlling tuberculosis infection.⁹ Other data suggest that hyperglycaemia also impairs the function of the innate immune system which is pivotal in combating the tuberculosis pathogen.^{10,11} Neutrophils from people with tuberculosis and diabetes mellitus have been shown to have reduced chemotaxis and oxidative-killing potential, compared to that in non-diabetic controls.¹² Leukocyte bacteriocidal activity is diminished in people with diabetes mellitus, especially those with poor glucose control.¹³ Patients with diabetes mellitus with poorer glycaemic control appear to be at a higher risk of tuberculosis.^{14,15} This demonstrates a dose-response relationship between the degree of hyperglycaemia and vulnerability to tuberculosis.

Taken together, these studies strongly support the hypothesis that diabetes mellitus directly impairs the innate and adaptive immune responses that are necessary to counter the proliferation of tuberculosis. The relative contribution of other factors, such as pulmonary microangiopathy, renal dysfunction and vitamin D deficiency remains to be established.¹⁰ Diabetic autonomic neuropathy may also increase the coughing threshold, which in turn might enhance the susceptibility of patients with diabetes to tuberculosis. Autonomic neuropathy could play a role in decreasing the ability of patients with diabetes to clear the bacterial load, as well as impairing their capacity to combat the tuberculosis pathogen.¹⁶

Causal association: tuberculosis increases the risk of diabetes mellitus

While evidence clearly suggests that diabetes and insulin resistance play a role in the development

of tuberculosis, the extent to which tuberculosis increases the risk of diabetes mellitus in people without diabetes has not been clearly defined. Some data suggest that patients with tuberculosis may be at increased risk of diabetes.¹⁶⁻¹⁸ Certainly, the stress of severe chronic infection leads to increased insulin resistance and increased insulin demand that may unmask an underlying β cell deficiency, leading to hyperglycaemia.¹¹ However, in most instances the resulting hyperglycaemia is reversible and resolves once the infection is treated. Inevitably, hyperglycaemia will progress to full-blown diabetes in some individuals, especially those who have other risk factors that are common to both diabetes mellitus and tuberculosis, e.g. tobacco smoking, alcoholism and poor nutrition.⁶ More research is necessary to explore the impact of *M. tuberculosis* on insulin sensitivity and the role of tuberculosis in diabetogenesis.

Clinical presentation

The clinical features (and presentation) of tuberculosis in most patients with diabetes are similar to those in patients without diabetes. However, patients with type 2 diabetes mellitus and tuberculosis are usually 10-29 years older than those without diabetes mellitus. A higher frequency of smear-positive disease has been reported in patients with type 2 diabetes aged 60 years and older.¹⁹ Furthermore, diabetes mellitus is associated with increased body weight. In a recent study in West Africa, 23% of patients with tuberculosis and diabetes mellitus were obese, compared to only 3% of patients without diabetes.²⁰ In Indonesia, 53% of patients with tuberculosis and diabetes mellitus weighed more than 50 kg before treatment started, compared to only 16.5% of patients without diabetes.²¹ There are no data to suggest any gender discrepancy and risk of developing tuberculosis between men, and women, living with diabetes.

Notably, coughing may not be a reliable sign of pulmonary tuberculosis in patients with diabetes with advanced disease and concomitant autonomic neuropathy, since the latter impairs one's innate coughing reflex, thus masking the early signs of tuberculosis infection.¹⁶ Extrapulmonary involvement appears to be less common in patients with diabetes mellitus and tuberculosis than it is in patients without diabetes who have tuberculosis.²²⁻²⁴ However, diabetes is associated with an increased risk of certain rarer, extrapulmonary manifestations, such as laryngeal tuberculosis.²⁵ The extrapulmonary symptoms of tuberculosis may also be missed or attributed to other diseases since patients with diabetes frequently have target organ damage with associated symptoms. Therefore, a comprehensive history should be obtained with regard to new cases when patients have both

tuberculosis and diabetes mellitus. Given that the risk of tuberculosis increases with decreasing glycaemic control,²⁶ it is also important to determine the severity of the diabetes and the presence of end-organ damage in patients in whom potential tuberculosis is suspected.

The focus of the physical examination should be directed towards detecting diabetes complications, including those pertaining to pulmonary tuberculosis, i.e. pleural and laryngeal involvement, and evidence of extrapulmonary and disseminated disease, for example, meningitis, lymphadenopathy, organomegaly, peritonitis and joint disease. It is important to search for macro- and microvascular complications of diabetes. Monitoring visual acuity during tuberculosis treatment is also important, especially in those with pre-existing diabetic retinopathy, given that ethambutol can lead to optic neuritis.

Investigations

When resources allow, two important tests to perform in patients with diabetes mellitus who present with symptoms suggestive of tuberculosis are smear microscopy and chest radiography. Sputum smear positivity is seen more frequently in patients with diabetes than it is in those without it, as the pretreatment pulmonary bacillary load tends to be higher.²⁷ The incidence of cavitary disease is also reportedly higher in patients with diabetes than it is in those without it.²⁷

Most patients with diabetes who present with tuberculosis have typical radiographic findings on chest radiograph. One study in Malaysia found very few differences in the radiographical patterns of patients with diabetes and tuberculosis, compared to those of patients without diabetes mellitus.²³ However, other studies have found a preponderance of cavitary and lower-zone disease in patients with diabetes.²⁸ With increasing patient age, the basal distribution of disease and atypical presentations may increase.²⁹

Treatment: diabetes treatment in patients with diabetes mellitus and tuberculosis

The standard goals and methods of treatment of diabetes apply during antituberculous treatment. Unfortunately, glycaemic control often deteriorates during tuberculosis treatment. Suboptimal glycaemic control is invariably multifactorial, and relates to catabolism that is secondary to severe sepsis, suboptimal adherence and aggregate side-effects. However, the most important determinant of deteriorating glycaemic control is drug interactions which lead to subtherapeutic antidiabetic drug levels.² Rifampicin, a potent inducer of the cytochrome (CY)P450 enzyme system in the liver, leads to reductions in the levels of

several antidiabetic medications. Of the sulphonylureas, glibenclamide and gliclazide levels may be reduced by 39% to 70%, respectively,^{30,31} and pioglitazone levels by as much as 54% when administered with rifampicin.³² The drug levels of the meglitinides, repaglinide (57%) and nateglinide (24%)^{33,34} are also significantly reduced when co-prescribed with rifampicin. Isoniazid is an inhibitor of CYP2C9 and may lead to increased levels of certain sulphonylureas. However, the inductive effect of rifampicin generally outweighs the inhibitory effect of isoniazid on the same enzymes.³⁵ Full induction of CYP450 enzymes is achieved approximately a week after initiating rifampicin-containing treatment. The induction dissipates roughly two weeks after stopping rifampicin.

Given the impact of rifampicin on the levels of several antidiabetic drugs, it is essential that clinicians monitor glucose control closely after initiation of antituberculous therapy. Indeed, many experts advocate intensification of diabetes mellitus therapy for the duration of tuberculosis treatment, transitioning to insulin-based therapy for the duration of tuberculosis treatment. Insulin is degraded by hydrolysis through the action of an insulin-degrading enzyme, so it is unlikely that levels are affected by either rifampicin or isoniazid.³⁶ Notably, the metabolism of metformin is not influenced by antituberculous therapy either. However, approximately 30% of patients experience nausea when prescribed metformin in combination with standard antituberculous therapy. This, in turn, may lead to suboptimal adherence and poor treatment outcomes.³⁷

It is unlikely that pyrazinamide and ethambutol, the other first-line antituberculous agents, interact with any antidiabetic drugs. However, pyrazinamide interferes with urine ketone testing, and may therefore hinder accurate detection of ketonuria in patients with diabetic ketoacidosis. The use of gatifloxacin in the treatment of multidrug-resistant tuberculosis has also been associated with the impairment of glucose homeostasis and the development of hyperglycaemia in patients without diabetes.³⁸

Treatment: tuberculosis treatment in patients with tuberculosis and diabetes mellitus

Patients with pulmonary tuberculosis should receive standard tuberculosis treatment, consisting of four antituberculous drugs for two months (rifampicin, isoniazid, pyrazinamide and ethambutol), followed by two drugs (rifampicin and isoniazid) for another four months. Rifampicin is the cornerstone of tuberculosis treatment. Its action is dose dependent and the recommended dose is 10 mg/kg body weight,³⁹ which might be at the lower end of the dose-response

curve. High daily doses are probably more effective. In practice, most guidelines advise 450 mg/day for patients below 50 kg, and 600 mg for those above 50 kg. Considering that patients with diabetes are usually heavier and gain weight during tuberculosis treatment, adjustment of the drug dose, especially in the later phase of treatment, is highly relevant to patients with diabetes. Antidiabetic drugs do not affect the concentration of antituberculosis drugs.³⁵

Patients with diabetes with pre-existing renal disease are at increased risk of renal failure as a side-effect of antituberculosis therapy. Of the first-line tuberculosis drugs, only ethambutol is dependent on renal clearance. Therefore, dosing intervals should be increased in patients with a creatinine clearance of less than 30 ml/minute. Peripheral neuropathy is a common side-effect of isoniazid and a number of antiretroviral drugs, most notably stavudine. Thus, antituberculosis treatment, particularly in combination with antiretroviral treatment, may also aggravate peripheral neuropathy in patients with diabetes. Ethambutol-induced optic neuritis may be more difficult to detect in a patient with diabetic retinopathy. The consequences of even modest visual reduction owing to ethambutol have greater significance if vision is already impaired by diabetic complications.

Tuberculosis outcomes in patients with diabetes mellitus

Considerable evidence demonstrates that individuals with diabetes who are infected with tuberculosis have worse clinical outcomes than individuals without diabetes. In the era before insulin therapy, patients with type 1 diabetes mellitus and pulmonary tuberculosis had a very poor prognosis.⁴⁰ With the introduction of insulin in 1922, this changed, although the risk of developing tuberculosis (and the course of tuberculosis) is often more aggressive in patients with diabetes than it is in patients who do not have diabetes mellitus.

Patients with diabetes are more likely to be smear positive on diagnosis, and to remain positive at the end of one, and two, months of treatment.²⁴ They are also far more likely to have persistent sputum culture positivity after two months of treatment, independent of the extent of pulmonary disease.⁴¹ Furthermore, a recent systematic review of 33 studies found that diabetes mellitus increased the risk of treatment failure and tuberculosis relapse.⁴² In this analysis, patients with diabetes mellitus were four times more likely to develop a tuberculosis relapse than those without diabetes mellitus. Health facility exposure to tuberculosis, an important contributor to the total tuberculosis infection risk in people living with HIV,⁴³ may contribute to the risk of re-infection in patients with diabetes mellitus

because of repeated attendance at health facilities for diabetes management.

Available data from low tuberculosis settings suggest that diabetes mellitus also increases the risk of death from tuberculosis. Patients with diabetes are twice as likely to die from tuberculosis compared to individuals who do not have diabetes.⁴² However, most studies that have evaluated the impact of diabetes mellitus on deaths from tuberculosis were performed in industrialised countries^{22,44,45} where tuberculosis mortality tends to be lower than it is in African settings.⁴⁶ Consequently, it is difficult to generalise these findings to an African context where the tuberculosis burden is considerably higher. If diabetes mellitus has a negative effect on tuberculosis treatment outcomes, as the data suggest, the mechanism of action is less than clear. Nonadherence to tuberculosis treatment and drug resistance to *M. tuberculosis* are two of the most important risk factors for treatment failure and mortality. However, in two recent studies, adherence to tuberculosis treatment in patients with diabetes mellitus was similar to, or better than, that in patients with tuberculosis who did not have diabetes.^{21,23} Furthermore, patients with diabetes mellitus did not appear to be at additional increased risk of drug-resistant tuberculosis, despite the risk of tuberculosis and impaired cell immunity.⁴²

One explanation for higher rates of tuberculosis treatment failure and relapse are the lower plasma levels of some of the antituberculosis drugs in patients with diabetes.^{47,48} A recent pharmacokinetic study in Indonesian patients with tuberculosis and diabetes mellitus found that exposure to rifampicin was 50% lower in heavier patients with tuberculosis and diabetes mellitus, compared to that in patients without diabetes mellitus during the continuation phase of treatment.⁴⁹ However, in the same setting, during the intensive phase of tuberculosis treatment, intensive pharmacokinetic sampling among weight-matched patients with tuberculosis with, and without, diabetes, did not reveal any differences in the pharmacokinetic parameters of the tuberculosis drugs.⁵⁰ These apparently contrasting results may be because of the increased body weight of patients with diabetes during the continuation phase of treatment. Further studies are needed to examine why diabetes mellitus places patients with tuberculosis at higher risk of death, and if patients with tuberculosis and diabetes mellitus, especially heavier ones, need higher doses of antituberculosis drugs. While it has also been argued that prolonging the standard tuberculosis treatment regimen for people with diabetes mellitus may improve outcomes, at present, little data exist to support this claim.⁵¹ There are also no data on the effectiveness and feasibility of early case detection and chemoprophylaxis of tuberculosis in patients with diabetes.

Public health implications

The burden of disease from diabetes and tuberculosis in southern Africa is significant. In South Africa alone, there was an incident rate of nearly 400 000 cases in 2011.⁵² Furthermore, it is estimated that there are nearly two-million South Africans with diabetes,¹ although up to 50% of these are undiagnosed. Given these facts, screening patients with diabetes for tuberculosis, and patients with tuberculosis for diabetes, should be a public health priority. Unfortunately, despite the fact that the World Health Organization strongly advocates a "bidirectional" approach to tuberculosis and diabetes mellitus screening⁵¹ (Table I), such practices are not widely implemented.¹⁶ Furthermore, the most effective and cost-effective means of screening patients with tuberculosis for diabetes mellitus and vice versa remains to be determined.

National tuberculosis control programmes and diabetes programmes in southern Africa are already overburdened and under-resourced. Recent studies have demonstrated that many primary care facilities have very limited capacity to accurately diagnose tuberculosis or diabetes. A 2005 study reported that only 6% of health centres surveyed in Mozambique, and 25% in Zambia, were capable of testing blood glucose levels.⁵³ Adding diabetes screening to the tuberculosis agenda, and vice versa, may be perceived as overwhelming by many public health programmes. However, better coordination and pooling of resources may also create mutual benefits. While the relationship between diabetes mellitus and tuberculosis is complex and requires careful attention and research, it represents an opportunity to strengthen areas of health service delivery, as well as achieve the greater goal of general health system improvement.

At the very least, an economically viable and locally feasible approach might include screening new patients with diabetes for symptoms of tuberculosis and referring those who screen positive for appropriate investigations. It could also extend to documenting self-reported diabetes mellitus in new patients with tuberculosis, and where feasible, performing a finger-stick glucometer assay on new patients with tuberculosis when initiating antituberculous therapy.

Conclusion

Increasing diabetes prevalence across southern Africa represents a significant threat to tuberculosis prevention and control, given the high burden of tuberculosis in this setting. Diabetes is associated with an increased risk of tuberculosis treatment failure, relapse and death. Poor glycaemic control, possibly exacerbated by tuberculosis and antituberculous therapy, is an important contributing factor to case fatality and relapse. Clinicians need to be aware of the clinical and pharmacological challenges when co-managing these complex diseases.

Conflict of interest

No conflict of interest is declared.

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Table I: World Health Organization recommendations for the care and control of diabetes and tuberculosis

World Health Organization recommendations	
Co-ordination	A joint plan for diabetes and tuberculosis activities should be coordinated at regional, district, and/or local level
Awareness	Healthcare workers, together with the population served, should be made aware of the interaction between tuberculosis and diabetes
Screening*	<i>At diabetes diagnosis and every follow-up visit:</i> Patients with diabetes mellitus should be asked about a cough lasting > 2 weeks <i>At diabetes diagnosis and every follow-up visit:</i> Clinicians should consider tuberculosis in patients with diabetes mellitus who present with a persistent fever, weight loss and night sweats
Referral	Patients with positive symptoms should be examined as per national guidelines** There should be an established referral system in place so that patients suspected of having tuberculosis can promptly receive diagnostic tests and treatment
Treatment	Patients with diabetes and tuberculosis should be treated according to existing tuberculosis treatment guidelines and international standards. Patients with tuberculosis and diabetes should be managed the same as patients who do not have diabetes

*: Recommended when the estimated tuberculosis prevalence exceeds 100/100 000 population

** : Standard approach: Sputum smear microscopy ± chest radiography if pulmonary tuberculosis is suspected

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