REVIEW

Tuberculosis and Diabetes Mellitus Co-Morbidity: Lessons to Learn From HIV/AIDS

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ABSTRACT

Tuberculosis (TB) and Diabetes mellitus (DM) are among the top ten causes of morbidity and mortality globally, with the Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) also causing significant mortality as well. The HIV-TB link has been well recognized since the beginning of the HIV epidemic, but link between TB and DM has only returned to the fore-front recently after effective treatments for each condition reduced the association that was reported earlier in the twentieth century. Recently also, urbanization, increasing age and sedentary lifestyle has led to an increase in diabetes prevalence. Diabetes mellitus is associated with a 3-fold incident risk of tuberculosis and, to a lesser extent, tuberculosis may also increase the risk of developing diabetes. Both diseases interact negatively at multiple levels, exacerbating and worsening the outcomes of the other.

The impact of these co-morbidities particularly in developing countries of Sub Saharan Africa, of which Nigeria is one, is likely to be large. An increasing prevalence of diabetes mellitus may hinder efforts aimed at tuberculosis control, making successful TB treatment and control more difficult. Improved management of tuberculosis and diabetes could build on the successes of the TB-HIV/AIDS collaborative activities, and DOTS strategy, which emphasizes support to patients, as well as a reliable supply of quality-assured medicines. This review aims to examine the association between these two important diseases, and explore ways to manage and reduce mortality caused by the duo.

Keywords: Tuberculosis, Diabetes, HIV, Co-morbidities

INTRODUCTION

Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), Tuberculosis (TB) and Diabetes mellitus (DM) are among the top causes of mortality globally, TB and DM being among the top ten[1]. Among these three are two chronic communicable diseases, HIV/AIDS and TB; and one non-communicable disease, DM. Infectious diseases in sub-Saharan Africa are the cause of appreciable mortality in the region. They constitute about 70% of deaths while chronic non-communicable diseases constitute about a quarter of deaths[2].

There is an association between communicable and non-communicable diseases which has been known for centuries, but was neglected until only recently when the burden of non-communicable diseases (NCDs) began to rise[3,4]. When the acquired immune-deficiency syndrome (AIDS) was first reported in 1981, it was not realised that the magnitude of the then impending epidemic would be huge, or that the most burden would be in sub-Saharan Africa. About thirty years later, it became obvious. In 2009, about one third of all persons living with HIV/AIDS (PLWHA), one third of all new infections and one third of all AIDS-related deaths occurred in about 10

countries in Africa, including Nigeria[5]. Now, the prevalence of non-communicable diseases has emerged as the next twenty-first century global epidemic. These diseases are becoming the leading causes of death and disability worldwide, and would be responsible for over three-quarters of global deaths by 2030[5].

People living with chronic communicable diseases are most likely to develop co-morbidity with non-communicable diseases, and co-existing communicable and non-communicable diseases increase the risk for each other, as well as the effect and outcomes of each other[6]. In particular, non-communicable diseases interact adversely with tuberculosis by increasing the vulnerability of individuals to TB infection, the risk of adverse treatment outcomes and the likelihood that the epidemic will be sustained within the population[7].

The response to the earlier HIV-associated TB epidemic was slow and not coordinated, despite warnings about the scale of the epidemic. The same slow response must be avoided with diabetes and TB. Traditional single disease approaches to global health which has been the mainstay of disease management need to be reassessed, with greater emphasis placed on multidisciplinary collaboration between health care workers, and integrated strategies for managing dual burden of diseases which many patients live with.

TUBERCULOSIS

Tuberculosis (TB) is an infectious bacterial disease caused by the tubercle bacilli, which belongs to the genus *Mycobacterium (Mtb)*. TB most commonly affects the lungs, and it is a leading cause of death among bacterial diseases. Currently, about twenty-three percent of global population is latently infected with tubercle bacillus *Mtb*, placing such individuals at a 5–10% average risk of developing active TB in their life time[8,9]. This may, however, be higher among people who have other risk factors, especially those causing immune-suppression. Active TB is defined as TB where the infection is active, organisms are usually detectable by culture-based or other molecular methods, the patient usually has symptoms and can transmit the disease to others. In latent TB infection on the other hand, the infection is dormant, organisms are not detectable by culture-based methods, the patient is asymptomatic and cannot transmit the disease to others.

Tuberculosis remains a major global source of morbidity and mortality. In 2017, there were an estimated 10 million new TB cases globally, with an associated 1·6 million deaths[8,10]. Majority of these cases occurred in population-dense regions of Africa and Asia where tuberculosis is endemic. According to the World Health Organization (WHO), in 2016, Nigeria ranks first in Africa and fourth out of 30 high burden countries which accounts for 87–92% of global TB burden[11]. The WHO tuberculosis case-notification data in 2017 also reported Nigeria as having a total of 233 incident TB cases, and 81 mortality cases per 100,000 population[8], thus making her a high burden TB prevalence country. High TB prevalence countries are defined as countries with greater than 100 TB cases per 100,000 population[12].

Tuberculosis may occur in the lungs (pulmonary) or outside the lungs (extrapulmonary), and both may also co-exist in a patient. The signs and symptoms of active TB include: cough that lasts for about three or more weeks, haemoptysis, chest pain, or pain with breathing or coughing, unintentional weight loss, fatigue, fever, night sweats, chills and loss of appetite. Without treatment, a person with TB disease will become gravely ill, and be able to transmit the infection to others. Untreated TB can become a life-threatening disease, but with effective and complete treatment, TB can be cured.

TUBERCULOSIS AND HIV /AIDS

The association between Tuberculosis (TB) and the human immune deficiency virus (HIV) was well recognized, since the early

years of the HIV epidemic. This association affects all aspects of both diseases, from pathogenesis and epidemiology to clinical manifestation, treatment, and prevention[4]. The greatest burden of the TB-HIV co-infection was observed in sub-Saharan Africa due to the high prevalence of both diseases in the region. Individually, both HIV and TB are two leading causes of infectious disease associated mortality worldwide.

HIV destroys the immune system of the infected individual and increases susceptibility to many infectious diseases including tuberculosis. It is the most potent factor known to increase the risk of progression of latent tuberculosis infection to active tuberculosis disease[13].

This has been shown to be very apparent in developing countries especially sub-Saharan Africa, where HIV has been responsible for an unprecedented increase in TB case notifications and for derailing TB control efforts. HIV-TB co-infection occurs either when people infected with latent TB acquire HIV infection, or when HIV infected people acquire new TB infection. In both cases, the risk of developing active TB increases several fold.

A latently infected person with Mycobacterium tuberculosis who is HIV negative, has an approximately 10% lifetime risk of developing active tuberculosis, whereas if such a person is HIV positive, the risk increases to about 30%. Tuberculosis is the most important life-threatening opportunistic infection associated with HIV infection. It is the leading cause of death among people living with HIV/AIDS, and about a quarter of deaths among people with HIV is attributed to TB. According to the recent WHO's global tuberculosis report, about one million new TB cases were estimated among HIV positive patients in 2017, and the African region accounts for about two-thirds HIV positive TB cases and TB deaths among them[8].

The diagnosis of TB in HIV infected patients is often difficult because their sputum smear examinations tend to be more frequently negative particularly in the late stages of HIV infection, X-ray abnormalities are often atypical, and their tuberculin skin tests are often negative due to immunosuppression. Therefore, people living with HIV/AIDS need early diagnosis and treatment of active TB disease, or preventive therapy if they are not already infected with TB.

THE DIABETES EPIDEMIC

Diabetes mellitus (DM) is a group of metabolic diseases characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both. It is a chronic condition that occurs when the body cannot produce enough insulin it requires or when it cannot effectively utilise the insulin it produces. This results in high levels of glucose circulating in the blood stream (hyperglycaemia), causing tissue damage over time[14]. Classic symptoms of DM include polyuria (excessive and frequent urination), polydipsia (excessive and increased thirst), polyphagia (excessive hunger or increased appetite) and weight loss. The condition is usually life-long, irreversible and associated with acute complications, as well as long term complications affecting several organs of the body if not well managed.

DM was first recognised in 1500 BC by the ancient Egyptians. Thereafter, Greek physicians adopted the term diabetes mellitus to describe the condition where persons affected lost weight and urinated 'sweet tasting urine' excessively[15].

According to the World Health Organization (WHO, 2006a) and the American Diabetes Association (ADA), DM is currently classified as Type 1 DM, Type 2 DM, Gestational diabetes mellitus (GDM), and a number of less common diseases such as latent autoimmune diabetes in adults (LADA), and maturity-

onset diabetes in the young (MODY)[16,17]. It is a chronic disease affecting millions of people in sub-Sahara Africa. It is fuelled mainly by globalisation, urbanisation, population growth, sedentary lifestyles and rural to urban migration.

Diabetes prevalence, deaths attributable to, and health expenditure due to the disease continue to rise globally. In 2017, the International Diabetic Federation (IDF's) most recent estimates indicate an estimated 451 million people living with diabetes. This number is predicted to rise to 693 million by 2045[18]. Nigeria was also said to have the third highest burden of DM in Africa[19]. Many people remain undiagnosed, while many that are diagnosed do not achieve proper disease control. With about 80% of the total number of people affected living in low- and middle-income countries, where the epidemic is gathering pace at alarming rates, the IDF Diabetes Atlas' figures also provide a worrying indication of the future impact of diabetes as a major threat to global TB control[18].

DIABETES MELLITUS AND TUBERCULOSIS CO-MORBIDITY

The association between Tuberculosis and Diabetes mellitus was well known and documented by Avicenna[20], dating back to the early 20th century. It was later forgotten when effective treatment and public health measures became available for both disease conditions, making the association less relevant[20]. This was more so as TB was less prevalent in high income developed countries where DM was more prominent, while DM was less prevalent in low and middle income (LMIC) developing countries where TB was more prevalent. Recently however, this association has re-emerged with the increasing prevalence of DM in LMICs coupled with a slower decline in global TB incidence rates. The relationship between DM and TB is bi-directional in the sense that diabetes may lead to the development of new tuberculosis cases, and to a lesser extent, tuberculosis may lead to the development of new diabetes cases[24]. Also, a large pool of latently TB infected people are likely to contribute to a growing proportion of future tuberculosis cases.

DM is a known risk factor for the development of tuberculosis infection and the reactivation of latent TB. People living with DM have a three-fold risk of developing active TB compared to people without DM[3]. Depending on the prevalence of TB in an area, there is a 5-30% higher risk of developing TB in patients with DM, when compared to people without DM.

The figure below (Fig 1) depicts the contribution of DM to TB prevalence in low and high incidence areas. Likewise, the longer the duration of, and the more the severity of DM in individuals, the more the risk of developing tuberculosis. The risk of developing tuberculosis is also higher among patients who can only achieve glycemic control while on insulin injection, particularly, those who have poor glycaemic control and need higher doses of Insulin for control.

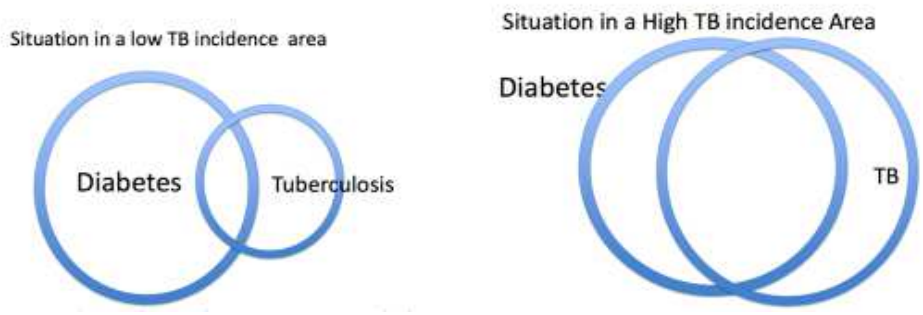

Figure 1: Contribution of diabetes mellitus to the TB epidemic

The risk of developing tuberculosis is also higher among patients who can only achieve glycemic control while on insulin injection, particularly, those who have poor glycaemic control and need higher doses of Insulin for control. Additionally, risk to DM is stronger in the presence of other risk factors, and more with type 2 DM than type 1 DM patients, since they are in the majority[21,22]. DM is also an important risk factor for MDR-TB, which is quietly fuelling the spread of tuberculosis, and this association between the two diseases may be the next challenge for global tuberculosis control worldwide.

On the other hand, the presence of TB in a patient may induce infection or stress-related hyperglycaemia which may manifest as transient, impaired glucose tolerance (IGT)[23]. This usually happens at TB diagnosis or when starting anti-TB therapy. It however resolves in most patients during the course of therapy, but leaves a significant risk of developing type 2 DM later in life[23].

Demographic characteristics are sometimes similar and associated with both diseases inter relatedly (Fig 2). Alcohol intake, smoking, hard drug intake and exposure to infectious cases all predispose patients to developing TB, while family history, age, occupation, educational and employment status predispose to dual disease[24]. Exposures to infectious cases takes place within family settings and certain occupations also increase rates of TB.

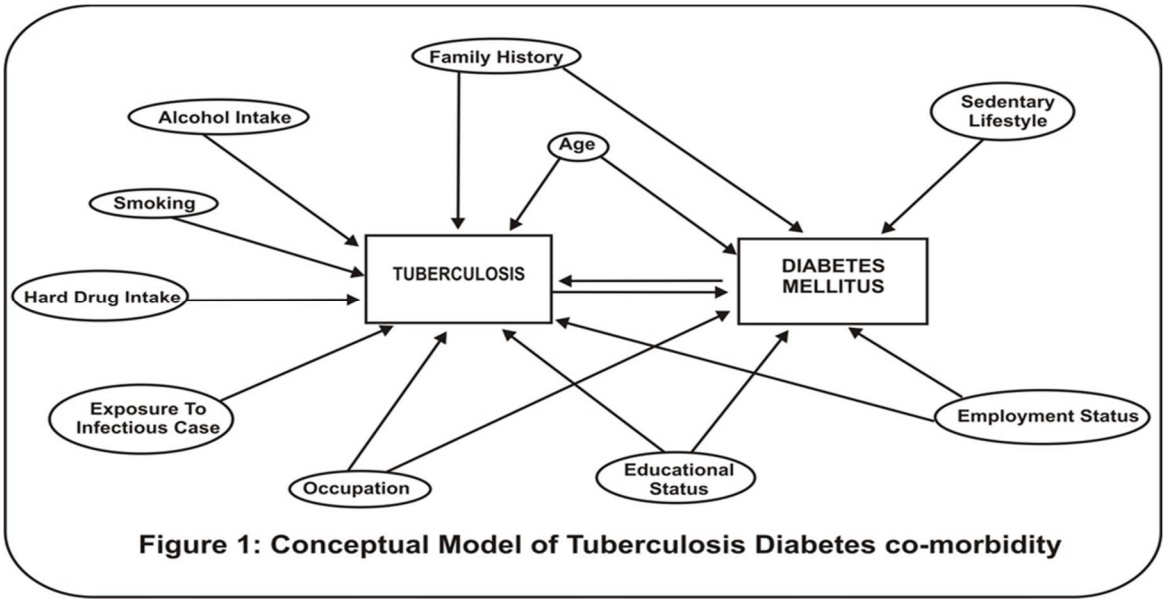

Figure 2: Tuberculosis Diabetes co-morbidity

Age has an inverse association with TB and DM. The older a person gets, the more immunity reduces, and the more susceptible they become to developing TB and/or DM. Also, the more education a person acquires, the more inclined they are to healthy living and employment which reduces risks of TB and DM, vice versa. Associated with this is the more sedentary occupation or lifestyle, the more risks of developing DM.

Both diseases interact negatively with each other, causing mutual exacerbation and worsening outcomes[25]. Diabetes worsens the clinical course of TB, and TB worsens glycaemic control in people living with diabetes. Patients with both TB and DM typically present with more frequent and severe symptoms and signs. Thus, TBDM co-occurrence is associated with increased risk of TB treatment failure or relapse, and higher mortality rates when compared with

patients with TB only[26]. TB infection in diabetic patients also affect glycaemic control adversely, leading to poor or inadequate glycaemic control, or making glycaemic control more difficult to achieve without proper management. In addition, TBDM patients may also take longer to respond to TB treatment, remain sputum positive for longer periods after treatment initiation, and are more likely to develop multi-drug resistant TB compared with patients with TB only[26,27].

As it was with HIV/AIDS when the epidemic first started, the scale of the diabetic epidemic is probably being underestimated, as many TBDM co-infected cases currently go undetected, progressing towards complications and unfavourable treatment outcomes unaware. At the same time established cases with co-infection are not being managed collaboratively for favourable optimal outcomes for each disease state.

THE COLLABORATIVE CARE MODEL FOR THE MANAGEMENT OF DM IN NEWLY DIAGNOSED TB PATIENTS.

One of the important milestones in the fight against HIV and TB was the publication and dissemination of the WHO Interim Policy of Collaborative HIV and TB Activities in 2004 which was set up to reduce the joint burden of the two diseases[28]. The policy goal of the ensuing collaborative TB/HIV activities was to decrease the burden of tuberculosis and HIV in populations affected by both diseases, while the objectives were:

1. To establish the mechanisms for collaboration between tuberculosis and HIV/AIDS programmes
2. To decrease the burden of tuberculosis in people living with HIV/AIDS and
3. To decrease the burden of HIV in tuberculosis patients.

The table below (Table 1) summarises the activities for the joint collaboration.

Table 1: Recommended collaborative TB/HIV activities

S/N	OBJECTIVES	ACTIVITIES
1	Establish the mechanisms for collaboration	**I.** Set up a co-ordinating body for TB-HIV activities effective at all levels **II.** Conduct surveillance of HIV prevalence in TB patients **III.** Carry out joint TB-HIV planning for resources, capacity building, communication, community participation and operational research **IV.** Conduct monitoring and evaluation
2	Reduce TB burden in persons living with HIV/AIDS	**I.** Establish intensified TB case finding for all cases **II.** Introduce isoniazid preventive therapy **II.** Ensure TB infection control in health care and congregate settings
3	Reduce HIV burden in TB patients	**I.** Provide HIV testing and counselling **II.** Introduce HIV prevention methods **III.** Introduce cotrimoxazole preventive therapy **IV.** Ensure HIV/AIDS care and support **V.** Introduce antiretroviral therapy

Since the epidemiological interactions and the effects on clinical presentation and treatment resulting from the interaction between diabetes and TB are similar to those observed for HIV and TB, the lessons learned from approaches to reduce the dual

burden of HIV and TB, and especially the modes of screening for the two diseases, can be adapted and applied to the screening, diagnosis, treatment and prevention of diabetes and TB.

As such, in 2011, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (The Union) recommended a collaborative framework for the clinical management and control of TBDM comorbidity in order to improve early diagnosis, treatment and health outcomes of both conditions[29,30]. This framework provisionally recommends screening for DM in people diagnosed with TB, screening for TB in diabetic patients, and promotes enhanced collaboration between TB and DM prevention and care programs without the establishment of a new specialist or independent control programme. The framework has many similarities to, and is to follow the pattern of the effective collaboration between TB and HIV/AIDs programs that avoided unnecessary duplication of service delivery and optimized use of health resources[28].

Fashioned after the TB/HIV framework, the objectives of the TBDM collaborative activities are:

1. To establish mechanisms of collaboration between diabetes and TB programmes;
2. To improve detection and management of TB in patients with diabetes; and
3. To improve detection and management of diabetes in TB patients.

The recommended activities are listed in table 2.

Table 2: Collaborative activities to reduce the dual burden of Diabetes and Tuberculosis

S/N	OBJECTIVES	ACTIVITIES
1.	Establish mechanisms for collaboration	**I.** Set up means of coordinating diabetes and TB activities
		II. Conduct surveillance of TB disease prevalence among people with diabetes in medium and high TB burden settings
		III. Conduct surveillance of diabetes prevalence in TB patients in all countries
		IV. Conduct monitoring and evaluation of collaborative diabetes and TB activities
2.	Detect and manage TB in patients with diabetes	**I.** Intensify detection of TB among people with diabetes
		II. Ensure TB infection control in health care settings where diabetes is managed
		III. Ensure high-quality TB treatment and management in people with diabetes
3.	Detect and manage diabetes in patients with TB	**I.** Screen patients with tuberculosis for diabetes
		II. Ensure high-quality diabetes management among TB patients

First, routine screening among diabetic patients to detect those having symptoms of TB is done in the diabetic clinic by enquiring from the patient if they have or have experienced symptoms related to TB, such as cough which has persisted for three or more weeks, unexplained weight loss, fever, night sweats and/or glandular swelling that might indicate extra pulmonary TB. Where this is the case, such patients should be promptly referred to the TB Directly Observed Therapy, Short Course (DOTS) clinic for appropriate diagnosis for TB and prompt management.

The same procedure should be carried out among newly diagnosed TB patients in the DOTS clinic, to identify those who are already known DM patients prior to developing TB, or those who will be newly diagnosed with DM. To detect new DM patients in particular, a rapid point of-care test is essential to quickly identify those who may have DM. TB patients who should be considered for DM screening include those aged 40 years and above, those who are overweight or obese, those who have a family history of DM, and those who have had previous gestational DM or have been previously prediabetic[12]. Screening is easiest and best done at the time of TB diagnosis, as it will guarantee and increase the chances of appropriate DM diagnosis, management and good glycemic control all through the duration of TB treatment, as well as guaranteeing favourable TB treatment outcomes.

Currently, most patients with co-morbid TB and DM are managed separately, for TB in DOTS clinic, and for DM in endocrinology clinic. However, a collaborative or integrated management that will entail the management of both diseases in a single clinic has been suggested as a better option. Just as the TB–HIV patient is managed in one single clinic for both diseases, management for the TB-DM patient can be situated together preferably in the TB clinic, and DM care administered from there, either until the end of the initial intensive phase of treatment, or for the whole duration of the anti-tuberculous treatment[12, 31]. This will ensure that the patient have access to the supportive directly observed treatment offered in the TB clinic, as well as advice about diet, exercise and drugs for DM. In addition, transmission of *Mycobacterium tuberculosis* within the diabetic clinic setting will be eliminated. On completing anti-tuberculosis therapy, diabetic patients should be referred permanently to the DM clinic for continued DM care, with vigilant follow-up to ensure glycemic control and prompt identification of possible recurrent TB.

CONCLUSION

The burden of diabetes mellitus is increasing worldwide, and its association with tuberculosis and its impact in Sub Saharan Africa is being recognised as likely to be a substantial one. Increasing prevalence of diabetes may hinder efforts aimed at tuberculosis control, increase the number of susceptible individuals in high burden tuberculosis countries, and make successful treatment outcomes for both diseases harder. Thus, calls for proposals that diagnosed TB patients be systematically screened for diabetes at TB treatment initiation, and that diabetic patients be screened for TB when symptomatic has been made to ensure early detection and high-quality management of both diseases.

Improved management of tuberculosis and diabetes could build on the successes of the HIV/AIDS collaborative activities, and DOTS strategy, which emphasizes support to patients, supervision of treatment, a reliable supply of quality-assured medicines, and regular monitoring. This will encourage effective management of TB treatment outcomes in people living with diabetes and vice versa.

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