Review Article

Bangladesh national guidelines on the management of tuberculosis and diabetes mellitus co-morbidity (summary)

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ABSTRACT

Tuberculosis (TB) and diabetes mellitus (DM) have synergetic relationship. People with diabetes are 2–3 times at higher risk of getting active TB disease. On the other hand, TB or anti-TB treatment may cause glucose intolerance. The dual disease of DM and TB is more likely to be associated with atypical disease presentation, higher probability of treatment failure and complications. In most of the health-care delivery systems of the world, DM and TB are managed separately by two vertical health-care delivery programs in spite of clear interaction between the two diseases. Thus, there should be a uniform management service for TB-DM co-morbidity. Realizing this situation, Bangladesh Diabetic Samity (BADAS), a nonprofit, nongovernment organization for the management of diabetes in Bangladesh, with the patronization of TB CARE II Project funded by U.S. Agency for International Development (USAID), launched a project in 2013 titled BADAS-USAID TB Care II, Bangladesh with the goal of "Integrated approach to increase access to TB services for diabetic patients." One of the project objective and activity was to develop a national guideline for the management of TB-DM comorbidity. Thus, under the guidance of National Tuberculosis Control Program, of the Directorate General of Health Services, Government of the People's Republic of Bangladesh and World Health Organization (WHO), this guideline was developed in 2014. It is based on the existing "National Guidelines and Operational Manual for TB Control" (5th edition) and guidelines for management of DM as per WHO and International Diabetes Federations. Along with that, expert opinions from public health experts and clinicians and "Medline"-searched literature were used to develop the guidelines. These guidelines illustrate the atypical presentation of the TB-DM co-morbidity, recommendations for screening, treatment, and follow-up of these patients and also recommendations in case of management of TB in patients with kidney and liver diseases. Thus, these guidelines will be a comprehensive tool for physicians to manage TB in diabetic patients.

Key words: Bangladesh, co-morbidity, diabetes mellitus, guidelines, tuberculosis

Introduction

The association between diabetes mellitus (DM) and tuberculosis (TB) and their synergistic role in causing human diseases has been recognized for centuries. DM is not only a risk factor for TB but also influences the disease presentation and treatment response. On the other hand, TB/anti-TB medications might induce glucose intolerance or worsen glycemic control in people with DM.

We have a national guideline for the management of TB, with some highlights on the treatment of TB in some

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co-morbid conditions, but a detailed guideline is lacking. Thus, physicians often face difficulties in treating TB with other co-morbidities, particularly DM, kidney, and liver disease, especially regarding drug selection and dosage in patients with renal and hepatic impairment, duration of anti-tubercular treatment and follow-up in DM patients. Recently, the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease have acknowledged the need for international guidelines on the joint management and control of TB and DM and have published a provisional collaborative framework for the care and control of both diseases.[1]

Materials and Methods

This guideline was developed as part of the "Bangladesh Diabetic Samity (BADAS)-USAID TB Care II project, Bangladesh," for the management of patients with TB-DM co-morbidity. The basis of this guideline is the existing "National Guidelines and Operational Manual for TB Control" (5th edition). Along with that, guidelines for management of DM as per WHO and International Diabetes Federations were followed. To develop this guideline, two workshops were arranged with the participation of public health experts and renowned clinicians from concerned specialties of different institutions of the country. An extensive online search through "Medline" was made for literature review of original and review articles in English language, regarding management of TB-DM co-morbidity, using the key words-TB, DM, and management of co-morbidity.

Epidemiology

Several epidemiological studies revealed that subjects with diabetes are at 3 times higher risk of getting active TB disease compared to those without diabetes.[2] The burden of TB increases with duration of DM and poor glycemic control.[3] Diabetes makes a substantial contribution to the incidence of TB. Almost 15% of pulmonary TB (PTB) and 20% of smear positive PTB may be directly linked to diabetes.[4] On the other hand, TB can cause any form of glucose intolerance and lead to increased incidence of DM. In different studies worldwide, the prevalence of glucose intolerance in TB patient has varied from 2% to 40%.[5]

Pathophysiology

A probable cause of increased incidence of PTB in DM is a defect in host defenses and immune functions. The immune derangements predominantly involve the cell-mediated immunity.[6] Hyperglycemia favor the growth, viability, and propagation of tubercle bacilli and hamper host-resistance to infection and repair capacity.[7] Multiple pulmonary vascular and functional abnormalities have been documented in diabetics known as pulmonary microangiopathy; that can contribute to delayed clearance of and spread of infection in the host.[8]

On the other hand, several theories have been put forward to explain why glucose intolerance develops in TB patients. Some study suggested that glucose intolerance is not merely a reaction to acute tubercular infection but rather a prediabetic state. Acute severe stress, infection, inactivity, and malnutrition stimulate the release of stress hormones epinephrine, glucagon, and cortisol, which raise the blood glucose level. Plasma levels of interleukin-1 and tumor necrosis factor-alpha are raised in severe illness, which can stimulate anti-insulin responses.[9]

Diagnosis

DM may influence the clinical manifestations, radiological features, and sputum conversion rates of PTB patients.[10]

Clinical presentation of pulmonary tuberculosis in diabetic patients

This can be significantly different from that of TB alone. Weight loss and weakness is a feature of both TB and DM. TB should be considered in patients with DM, who have unintentional weight loss, night sweats, and general debility that cannot be fully explained by poor diabetic control.[11] Diabetic patients are more susceptible to have a more aggressive course of TB still having less clinical manifestations like fever or cough.[12] Compared to non-DM patients, they frequently present with complications such as lung abscess, pleural effusion, and hydropneumothorax.[13]

Radiological presentation of pulmonary tuberculosis in diabetic patients

PTB predominantly involves the upper lobes of lungs. Lower lung field TB may occur but is often misdiagnosed as pneumonia, bronchial carcinoma or lung abscess as these patients are often smear negative.[11] Chest X-ray images from patients having PTB with DM have been described as "atypical," mainly because they frequently involve the lower lung fields or multiple lobes, in the form of consolidation, nodular or patchy opacity, and cavitary lesion. Glycemic control can significantly influence the severity of radiographic manifestations of PTB in patients with DM. Cavitary lesions occur more in patients with uncontrolled blood glucose (HbA1c >7%).[14]

Microbiological features of pulmonary tuberculosis in diabetic patients

Compared to nondiabetic patients, the frequency of smear positive PTB is more in DM patients (BADAS-USAID TB

Care II Project, Bangladesh; unpublished report). There is evidence that TB patients with DM may have higher bacillary loads than patients with TB without DM.[15] This might be due to the presence of cavitary lesions in patients with uncontrolled diabetes. DM is an independent risk factor for delayed sputum clearance of mycobacteria during the first phase of anti-TB treatment, the time during which treatment is considered to render the patient noninfectious.[16] It was observed that an average of 5 day delay in mycobacterial clearance may occur within the first 60 days of treatment in diabetic patients compared to nondiabetics.[17]

Screening for tuberculosis–diabetes mellitus co-morbidity

Since DM and TB increase the risk of each other, there should be "bidirectional screening" for TB in diabetes patients and diabetes in TB patients.[18] Screening for active TB in DM clinics should lead to earlier detection of TB and reduce the risk of nosocomial TB transmission in DM clinics. Every DM patient should be enquired of a cough for more than 2 weeks, unexplained/unintentional weight loss, night sweats, fever, or history of contact with infectious TB patient. In suspected cases sputum for acid-fast bacillus (2 samples) including Gene X-pert should be done. In selected cases (if unable to produce sputum and in extra-PTB), other supportive tests such as Chest X-ray, complete blood count with erythrocyte sedimentation rate test, and tuberculin test may be needed.

On the other hand, TB increases the risk of diabetes, and antitubercular drugs, particularly rifampicin (R) and isoniazide (INH) can cause hyperglycemia.[19] Hence, screening for DM is recommended all adults older than 18 years with TB.[20] The preferred method of screening for DM is by 75 g oral glucose tolerance test. The best time of screening for diabetes in TB patient is at the time of diagnosis and initiation of TB treatment or 2–4 weeks after starting anti-TB therapy.[21]

Treatment of Tuberculosis–Diabetes Mellitus Co-morbidity

Treatment of tuberculosis in patients with diabetes

In general, patients with TB and DM are not treated differently than patients with only TB. Patients must be treated according to standard category.[22] However, this approach might need to be reconsidered considering individual diabetic patients disease status. Before initiation of anti-TB treatment in a patient with DM-TB co-morbidity, the following points should be considered clinical condition and extent of radiological involvement by TB, glycemic status of the patient, hepatic and renal function of the diabetic patient, presence of any diabetic complications like nephropathy or neuropathy, and possible drug interaction between anti-TB medications and oral anti-diabetic drugs (OADs).

Almost all the anti-TB drugs are safe in diabetic patients with TB without other comorbidity. Before starting anti-TB therapy, baseline renal, and liver function should be assessed. Careful and frequent monitoring is required as there is increased chance of hepatotoxicity, because a good number of diabetic patients have fatty liver with raised baseline liver enzymes, and many of them are already getting OADs having hepatic interaction. Many of the diabetic patients have associated nephropathy. In these patients dose modification of nephrotoxic anti-TB drugs, for example, ethambutol (E) and streptomycin (S) are required. There is increased risk of induction or aggravation of peripheral neuropathy in DM patient on anti-TB containing INH. Thus, it is recommended that diabetic patients should receive at least 40 mg/day pyridoxine to prevent INH-induced peripheral neuropathy.

Duration of treatment of tuberculosis in diabetes mellitus patients

The duration of treatment of TB in DM patients, in general, is according to treatment category and site of TB. However, the following factors must be considered to determine the ultimate duration of treatment clinical, microbiological, and radiological response of the patient to anti-tubercular therapy, extent of the tubercular pathology and glycemic control during the treatment course. Thus, the duration of TB treatment in a DM patient should be extended beyond 6 months up to 9 months or more in following situations-poor clinical response of patient (persistent fever, cough/sputum, weight loss), bilateral extensive cavitary lesions/parenchymal involvement of lung, delayed sputum conversion (sputum smear positive after 2 months), delayed radiological improvement, and poor glycemic control during treatment.[23]

Treatment of diabetes mellitus in tuberculosis patients

One of the most important aspects of a successful treatment of TB in DM patient is to achieve good glycemic control as early as possible and maintain it throughout the entire course of anti-TB treatment, without causing drug interactions or side effects. Strict glycemic control makes antitubercular drugs more effective. It is also required for better clinical, radiological, and bacteriological resolution of the disease. The glycemic target for a patient with co-morbidity of TB-DM is like that of DM itself.[24] However, individualized glycemic targets might be needed considering the age of the patient, duration of DM, risk of adverse events such as hypoglycemia, presence of co-morbidities such as nephropathy, neuropathy, and hepatic dysfunction.[25]

It is established that insulin is the preferred agent for control of diabetes in patients with TB.[26] Insulin has anabolic action, thus improves appetite and promotes weight gain in malnourished TB patients, apart from lowering the pill burden. Insulin is the best agent for fastest reduction of HbA1c. Many of the DM patients have coexistent nephropathy/hepatotoxicity with contraindication for OADs; thus, insulin is the best anti-DM medication in these patients. Insulin should preferably be given throughout the entire course of anti-TB treatment. If not, then must be given for at least the intensive phase of anti-TB chemotherapy. If a DM patient on insulin develops TB, then the dose of insulin should be adjusted as per requirement. If a DM patient on OADs develops TB, then the patient should be switched to insulin from OAD. If DM is newly detected in a TB patient, then the patient should be started on insulin for control of diabetes.

Follow-up of diabetes mellitus–tuberculosis patients

Frequent follow-up is required in a DM patient on anti-TB treatment to evaluate the treatment response, to determine the duration of treatment, for early detection of any adverse drug reaction or complication and early detection of treatment failure or relapse.

First, follow-up should be 3–4 weeks after starting anti-TB; to see the glycemic status and detect anti-TB induced hepatitis or hypersensitivity reaction. Second, follow-up should be at the end of 2 months; to see the clinical, radiological response, and sputum conversion rate. If the sputum smear is positive after 2 months, then the initial phase should be extended to 3 months and sputum for gene X-pert should be sent. Subsequent follow-up should be 2 months apart till the end of treatment. More frequent follow-up may be necessary in patients with nonalcoholic steatohepatitis, chronic kidney disease, uncontrolled blood glucose, and severe TB infection.

Conclusion

Since TB and DM are reciprocally related to each other and the dual burden has an atypical presentation, a bidirectional screening is necessary for early detection and treatment initiation.

The dose and duration of anti-TB treatment in a DM patient may need to be modified based on the response of patient and presence of other co-morbidities. Strict glycemic control with insulin is necessary. Careful monitoring and action is necessary to prevent adverse effects, treatment failure, and drug resistance.

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Conflicts of interest

There are no conflicts of interest.

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