

Several clinical tools, namely, multifocal electroretinography (ERG), flash ERG, contrast sensitivity, colour vision, short-wavelength automated perimetry, and OCT, can detect neuronal dysfunction at early stages of diabetes

## CONCLUSION

Diabetic retinopathy is the most common complication of diabetes which may lead to legal blindness and is a major public health problem. Early detection through screening, educating the population and timely intervention may decrease the complications in the course of disease.

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# Diabetes Mellitus and Tuberculosis

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**Abstract:** Diabetes and tuberculosis are the twin epidemics which has a major impact on morbidity and mortality of either disorder. Improved understanding of the bidirectional relationship is necessary to reduce the dual burden of the disease. The present article focuses on the association of the two disorders and salient features of the two disorders when they occur together.

## INTRODUCTION

Tuberculosis (TB) and diabetes mellitus (DM) are both important health issues more so in developing countries where TB is endemic and burden of diabetes is also very high. A bidirectional association between them has been demonstrated by many researchers. In early 20<sup>th</sup> century it was a major concern due to lack of proper treatment of both the diseases. With the resurgence of multi drug resistance tuberculosis, along with presence of human immune deficiency virus infection and epidemic of diabetes in these countries, this association has been a major concern in these areas<sup>1,2</sup>.

India not only faces the public health difficulties associated with newly increasing rates of chronic diseases such as DM, but as with other low and middle income countries, endures sustained rates of infectious diseases (such as TB) which remain to be brought under control.

Depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon gamma, pulmonary microangiopathy, and micronutrient deficiency

have been implicated in the occurrence of tuberculosis in Diabetic patients<sup>3</sup>.

## EPIDEMIOLOGY

In 2014, 387 million people have diabetes; by 2035 this will rise to 592 million. The greatest numbers of people with diabetes are between 40 and 59 years of age 179 million people with diabetes are undiagnosed. Diabetes caused 4.9 million deaths in 2014; Every seven seconds a person dies from diabetes. 77% of people with diabetes live in middle and low income countries the prevalence of Diabetes in India as per International Diabetes Federation (IDF) is 8.6%<sup>4</sup>.

Asia is the epicenter of the growing burden of DM and the largest contribution is from India and China<sup>5</sup>.

Tuberculosis (TB) remains a major global health problem. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease. India and China accounted for 39% of the incident TB patients in 2012.

Challenges to TB control and treatment success include structural factors, such as suboptimal case detection and non-adherence to therapy, as well as host-level factors, such as HIV and diabetes mellitus (DM), that increase vulnerability to active TB<sup>6</sup>.

Worldwide, 70% of diabetics live in TB endemic countries. In the 22 countries

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with the highest burden of TB, the prevalence of DM in the general population ranges from 2% to 9%<sup>7</sup> and eight of the ten countries with the highest incidence of DM are also classified as high burden countries for TB by the World Health Organization (WHO). Indonesia, with the third highest burden of TB in the world, has the fourth highest number of diabetics<sup>8</sup>. China, India, Peru and Russia are other countries that need to be given particular attention<sup>9</sup>.

Notably, pulmonary TB is the ninth most frequent complication of DM<sup>10</sup> and due to a rising prevalence of DM, the relative contribution of DM to the TB epidemic is increasing.

#### DIABETES AS RISK FACTOR FOR TUBERCULOSIS

Uncontrolled diabetes leads to a greater risk of developing TB, thus increasing prevalence of diabetes poses a great challenge for control of tuberculosis. A recent study has shown that, the countries where there is increase in prevalence of diabetes also had a significant increase in the number of people with TB<sup>9</sup>.

The association between diabetes and tuberculosis has been seen by several studies, and was found that people with diabetes are around 2.5 times more likely to develop tuberculosis<sup>11</sup>.

Few cohort studies have found relative risk of TB and DM to be 2.52 (95% CI: 1.53 to 4.03). The frequency of DM in tuberculosis patient was found to be 5.6%, 7.3% and 14.8% in India, Turkey and Indonesia respectively<sup>12-15</sup>.

Risk of TB was higher in younger people, more so in patients with type 1 DM. The greater incidence of tuberculosis is associated with uncontrolled hyperglycaemia. Correlation between active TB and the level of glycosylated hemoglobin (HbA1c) (hazard ratio 1.39, 95% CI: 1.18-1.63 per unit increase) has been shown in one study<sup>3</sup>.

Overall, the risk of tuberculosis attributed to diabetes is around 25%<sup>12</sup>. Acquired immunodeficiency syndrome (AIDS) is potent risk factor for TB as compared to DM, but as the frequency of DM is very high, the effect is equal or even greater than AIDS.

#### CLINICAL FEATURES

Tuberculosis progresses rapidly in diabetic patients and tuberculosis also follows an aggressive course in these patients. The spread or flare up of tuberculosis is associated with uncontrolled diabetes.

The clinical characteristics of TB do not differ among diabetic and non-diabetic patients has been documented in few studies. Extra-pulmonary involvement has also been reported to be less common among diabetic TB patients than in non-diabetics<sup>16</sup>. A higher mean HbA1c among TB-DM has been found, as compared to DM without TB<sup>3</sup> however in few studies the link is missing<sup>13</sup>.

Studies have shown that TB-DM patients are of older age (>45 yrs) with male preponderance. It has also been found that patients with diabetes who have symptoms of general ill-health like fever, weakness, apathy, cough, haemoptysis, and chest pain; investigations may reveal the presence of tuberculosis. It has also been found that if a patient who has been put on anti-tuberculosis treatment failed to respond adequately in a given period of time and further investigations sometimes may reveal the presence of diabetes<sup>12</sup>.

DM has been seen as an independent risk factor for numerous acid fast bacilli (AFB) on the sputum smear examination<sup>14</sup> however few studies does not reveal this association<sup>13</sup>. These conflicting results might be due to the control status of DM.

Thus it can be concluded that pulmonary tuberculosis should be considered in those patients with diabetes mellitus who have weight loss, fever and general debility that cannot be fully explained by poor diabetic control and diabetes should be considered in those patient with tuberculosis; in whom adequate response to anti-tuberculous treatment is not seen.

#### RADIOLOGICAL CHANGES IN TB-DM PATIENTS

Some studies did not find any difference between DM and non DM cases in respect to distribution of pulmonary involvement<sup>13</sup>. However, other studies demonstrated a higher incidence of lower lobe involvement among DM TB cases. (Fig 1) Diabetic patients showed a high prevalence of non segmental distribution



**Fig 1:** Chest Radiograph showing lower lobe involvement



**Fig 2:** Computed Tomography Scan showing lower lobe involvement and cavitory lesion

(30%) and multiple small cavitory nodular lesions. These cavitory lesions are more commonly seen in lower lobes<sup>17</sup>. (Fig 2) Factors related to cavitory lesions are uncontrolled DM and insulin dependency.

Thus chest radiograph images in TB-DM subjects significantly depart from the typical presentation with predilection of lower lobes and cavitory lesions.

#### SPUTUM CONVERSION RATE

TB-DM patients have a higher pre-treatment bacillary load and DM is supposed to be an independent risk factor associated with numerous AFB on sputum smear examination<sup>14</sup>. The high bacillary load in TB patients with DM could be explained by the immune suppression induced by DM. Studies have shown a trend toward increased time to sputum conversion Uncontrolled DM (HbA1c>7) appears to be a significant risk factor for positive sputum culture after two months of anti tuberculous treatment<sup>18</sup>. However if intensive phase of treatment is prolonged for one more month the sputum conversion is expected.

#### OUTCOME

DM may have a negative impact on the outcome of TB treatment: higher failure rates, higher rates of all-cause mortality and death specifically related to TB. Some studies have also reported higher relapse rate of tuberculosis in patients with diabetes<sup>19</sup>.

On the contrary, few recent studies have shown that the association of diabetes did not alter the response of pulmonary TB to treatment<sup>20</sup>. Failures, deaths, relapse rates and favorable outcomes (cured/treatment completed) were comparable in pulmonary TB patients with or without DM. It is also documented that in well-controlled diabetes the course of pulmonary tuberculosis is not different from that in patients without diabetes.

#### DRUG INTERACTION

Concentration of anti tubercular drug particularly, rifampicin, is lower in patients with diabetes<sup>21</sup>. This effect is probably associated with the severity of hyperglycemia. The exact mechanism is not defined, however a decrease in gastric hydrochloric acid secretion and impaired drug absorption, may be the reasons.

Rifampicin and isoniazid have hyperglycaemic effects. Rifampicin induces metabolism and decreases blood level of sulfonylureas, leading to hyperglycemia. It doesn't affect the metabolism of metformin or insulin. Pyrazinamide, also, may result in difficult control of diabetes<sup>16</sup>.

#### DRUG RESISTANCE

Some studies have found an increased risk of Multi drug resistance tuberculosis (MDR TB) among diabetics, ranging from 2.1 to 8.8 times<sup>22</sup>. Frequent relapse with resistant strains is also noted in diabetics. However a large number of studies have not found any relationship between MDR TB and diabetes<sup>18,20</sup>.

Thus, the relation between diabetes and MDR-TB remains unproven. More studies are needed to study the influence of diabetes on the incidence of resistance to antitubercular drugs. This is particularly relevant in a country like India having the highest pool of MDR-TB patients, coupled with the largest projected diabetic population.

## SCREENING

### *Tuberculosis in diabetics*

Screening for active TB among diabetics could improve case detection and could consequently lead to earlier therapy and prevent transmission of disease. The method for screening of TB is not yet defined, although performing chest X-rays at the time of DM diagnosis, and at regular intervals thereafter can be a possible method<sup>23</sup>. Any diabetic patient with suspicious symptoms such as cough for more than 2-3 weeks, weight loss, fever, or an abnormal imaging study should be investigated for presence of active TB. There is currently insufficient evidence for more active screening measures.

### *Diabetes in tuberculosis*

Screening for DM in patients with TB could improve case detection, early treatment, and prevention of DM complications. Best time for screening is not defined; some recommend screening at the onset and start of anti TB treatment, to ensure initiation of diabetes treatment, and correction of hyperglycemia, which potentially could have positive effects on the outcome of TB treatment<sup>23</sup>. Also patients with Tb are referred to peripheral centre where lab facilities are not available. Others recommend screening after 2-3 months of start of anti tuberculous treatment when the disease is stable as tuberculosis similar to other infections can cause hyperglycaemia which settles with adequate treatment and disease stabilization.

Due to these reasons, some recommend screening both at the time of diagnosis of TB and three months later after initiating treatment and disease stabilization<sup>24</sup>.

## TREATMENT ISSUES

### *Management of Tuberculosis*

It has been observed that conversion from a sputum smear positive state to smear negative state can be accomplished by anti-tuberculous chemotherapy. However, controversies exist regarding various issues in the management of pulmonary tuberculosis in the diabetic patients.

Few unanswered questions are that whether the initial treatment should include standard regimen (isoniazid, rifampicin, ethambutol and pyrazinamide) or should an additional drug (possibly a quinolone) be added to the initial regime to rapidly reduce sputum AFB load in view of higher relapse rate and delayed sputum conversion. The other question which is unanswered is that treatment duration should be for 6 months as per the standardized WHO regimen, or should their treatment be extended to a total of 9 months, as these patients might have an increased relapse rates<sup>25</sup>.

### *Management of Diabetes Mellitus*

Maintenance of blood glucose values at normal or near normal level, is one of the most fundamental aspects in patient care. As tuberculosis worsens the glycaemic control, maintaining the normoglycaemia in tuberculosis is a challenge<sup>26-27</sup>.

Whether this normoglycaemia be maintained with oral hypoglycemic agents or the use of insulin is mandatory in patients with pulmonary tuberculosis and diabetes is still an area of uncertainty. Insulin is a preferred agent as it is anabolic, improves appetite, and promotes weight gain. However normoglycaemia could be maintained with oral agents also.

Would tighter glycaemic control help in more effective action of the anti-tubercular drugs and faster clinical and radiological resolution? This is currently under investigations but is logical to do so.

## CONCLUSION

The burden of diabetes mellitus is increasing worldwide. The association of tuberculosis and diabetes is a challenge for tuberculosis control worldwide. The current diabetes epidemic may thus lead to a resurgence of tuberculosis in endemic regions like India. Improved understanding of the bidirectional relationship is necessary for proper planning to reduce the dual burden of diabetes and tuberculosis.

Focused and coordinated actions, like active case finding and treatment of latent tuberculosis in parts of the world where diabetes is epidemic and tuberculosis endemic, are needed to properly contain the dual disease. Conversely efforts to

diagnose, detect and treat DM may have a beneficial impact on TB control.

Prevention, screening, and treatment of both diseases together are more effective. Perhaps, a model similar to the TB-HIV program may be the best approach.

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