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Correlated Diabetes Mellitus and Tuberculosis: The Challenge Continues

Ankita Pandey, Shivangi P and Laxman S. Meena*

CSIR-Institute of Genomics and Integrative Biology, India

***Corresponding author:** Laxman S. Meena

laxmansm72@yahoo.com

CSIR-Institute of Genomics and Integrative Biology, India.

Tel: 011-27002200
Fax: 011-27667471

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Abstract

Co-relation between diabetes and tuberculosis (TB) creates dual burden of this disease worldwide. This bi directional association necessitates special attention and thus detailed study on human immune system regarding this is necessary. It is very important to develop some good strategies for prevention of diabetes in patients who are exposed to *Mycobacterium tuberculosis* (*M. tuberculosis*). Both these diseases are negatively affecting each other as individual with tuberculosis may frequently attain hyperglycaemic condition in diabetic patients and on the other side anti diabetic drugs may also interact with anti tuberculosis drugs in many ways to decreases their efficacy. This review provides recent estimates of TB and diabetes incidence and mortality in the world. In this review, we summarize the current clinical and immunological studies on co-relation between diabetes and TB and what can be done for prevention of these diseases, and spread awareness of this unfavourable co-relation between communicable and non communicable disease which can cause serious threat to public health.

Keywords: *Mycobacterium tuberculosis;* Alveolar macrophages; Pathogenesis; Diabetes mellitus; Phagolysosome

Abbreviations: TB: Tuberculosis; *M. tuberculosis: Mycobacterium tuberculosis*; DM: Diabetes Mellitus WHO: World Health Organization; IFN-γ: Interferon γ; IL: Interleukin; TNF-α: Tumour Necrosis Factor-α

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Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* H37Rv (*M. tuberculosis*) is one of the oldest known human disease whose risk increases day by day and become fatal [1,2]. Ability of *M. tuberculosis* to utilize macrophages for its replication enables it to survive and further cause disease [3]. There were 53 million cases of TB reported by WHO in all over world during 2000-2016. TB is the 9th cause of death worldwide and 1st in case of infectious disease [4]. Controlling TB is a global health issue which becomes more challenging because of its association with social and economic conditions [5]. *M. tuberculosis* has co-evolved with humans for years. TB detected in a fossil of Pleistocene bison is the oldest evidence of presence of *M. tuberculosis.* Robert Koch received a Nobel Prize in 1905 for the discovery of bacillus causing TB, *M. tuberculosis* [6]. The double burden of TB and diabetes has attracted much attention in the past decade. The co-relation between these two diseases is a serious threat to public health. Type 2 diabetic patients have a weak immune response and hence are prone to catch infections including TB. Almost one-third of the total population in the world is infected with *M. tuberculosis.* This bacterium remains inactive in some individual in the initial stage and in later stage of life it could become active and cause disease especially in people who suffers from diabetes [7,8]. Response of diabetic patients to initial phase of anti TB treatment is slow and almost 8-10% of tuberculosis cases are linked to diabetes all over the world. 2-3 fold culture positive TB is shown in some studies after 3 months of treatment [9,10]. Diabetes is co-related with failure of treatment in TB as well as deterioration of health after improvement. Disease control program will need to expand their efforts to cure patients with diabetes mellitus (DM) and TB [11,12]. This co- relation between DM and TB is one of the major concerns for immunologists and clinicians [13].

Literature Review

Factors associated with Diabetes Mellitus (DM) and Tuberculosis (TB)

Age- The data available regarding this factor is not enough to

conclude the extent of its contribution in diabetic TB patients. However, a case study in California and Mexico has shown decrease in association between DM and TB with increase in age [14,15]. Association of TB with DM is more dominant in younger population. DM patients who are using insulin are at higher risk of tuberculosis [16].

Sex- It is found that in some cases men have strong association but other suggests that there is higher risk in women. Relationship with sex varies by age and it is observed that higher proportion were women in older age and men in younger age. Although the association with sex is not very clear [14,17,18].

Prevalence

In the Middle East, prevalence of DM and TB is estimated to be 15.2 million people with positive diagnosis. It is expected that, this will be increasing around 42.6 million by 2030. Global report noted that every one person in three is infected [19]. In one of the study it has been found that, tuberculosis rate vary in diabetic patients between 1.6 and 2.8 millions. Tuberculosis is ten times common in diabetic patients in comparison to non diabetic patients [20]. Prevalence of TB in DM patients is higher in countries of Asia although the global prevalence is low. Former studies show higher prevalence of TB among diabetic patients in low and middle income countries [21,22]. Also it is reported that screening of TB among DM patients were detected with high rate of prevalent TB. According to a research it is clearly shown that the large population affected with TB are those in which TB is relapsed after having DM [23].

Poverty

Low income countries are more prone in catching infection of communicable disease. Though, the burden of non communicable disease found to be 47% in year 1990 and is predicted to be increased by 69% by year 2020 in low income countries [9]. Increasing rates of industrialization and urbanisation directs higher rates of obesity and diabetes. The number of people with diabetes, which was 171 million in 2000, is expected to grow to 366 million–440 million by 2030, with three-quarters of patients with diabetes living in low-income countries [24].

Non functional immunity to *M. tuberculosis* in DM patients

Macrophage activation by T cell inhibits *M. tuberculosis* replication and restricts this disease for life time in infected humans [25]. Conversion of active disease from inactive infection is higher with T-cell deficiency or loss of cytokine function (IFN-γ, IL-12, TNF-α). Immune cells and cytokines increase in circulation of diabetic patients co infected with tuberculosis [26]. Granulomatous sores are seen in various areas of the head and neck and a troublesome symptomatic test for the radiologist. Infective granulomas might be because of bacterial or parasitic operators. Non-infective granulomas are Wegener's granulomatosis, sarcoidosis, amyloidosis, compound granuloma and reparative goliath cell granuloma [27-29]. Current research suggests reduction in the association of monocytes with *M. tuberculosis* in diabetic patients which ultimately results in decreased opsonin and C3 component of the compliment system which play an important role in phagocytosis of the pathogen [30,31]. Cell mediated immune response is activated by efficient phagocytosis of *M. tuberculosis* which restrict its initial growth but this phagocytosis dramatically decreases in chronic diabetic patients and this delay subsequently plays an important role in increasing the risk of tuberculosis infection and persistence shown in **Figure 1** [32].

Discussion

Impact of diabetes on TB treatment

DM is often associated with *M. tuberculosis* clearance which is delayed during treatment in diabetic patients and sometimes treatment failure, relapse or death has also been reported [33]. The anti-TB drug therapy involves wide range of drugs, which can develop adverse drug reaction in patients. If we use anti DM medication, it can be interact with anti tubercular drugs. It is necessary to eliminate the factors which are associated with adverse reaction of anti TB medication which might leads therapy success [34]. DM has been associated with all mortality cases in patients having TB and mostly death is reported in case of pulmonary TB [35,36]. Drug toxicity, mainly in hepatocytes will increase due to diabetes therefore; death chances will be 6 times higher in diabetic TB patients [16].

Comparative study of TB patients with and without diabetes

If we compare diabetic individual with non diabetic, then we can see the dominance of re infection or relapse. We can conclude that anti tuberculosis drugs will fail to treat infection. Some evidences suggest that T cell response in diabetic patients is greater quantitatively but functionally it is less effective than the non diabetic patient's response as shown in **Table 1** [26]. Common

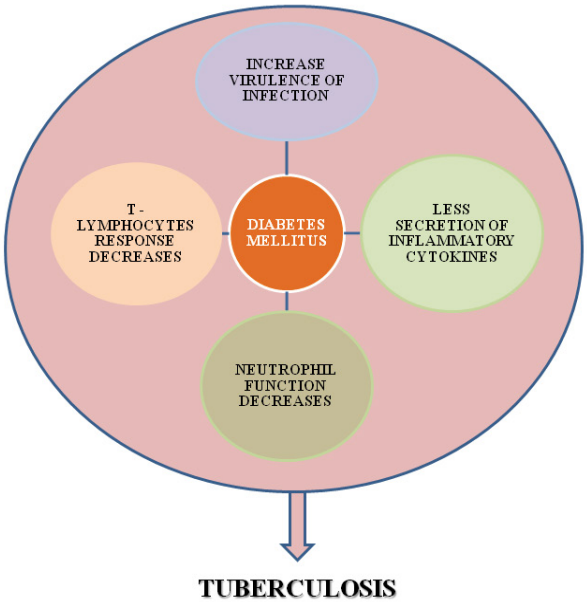

Figure 1 Immunological responses in diabetes mellitus which leads to tuberculosis-In diabetic patients, secretion of cytokines is less, T cell response reduces and due to this function of neutrophil decrease. All these conditions are lead to tuberculosis.

symptoms are almost same including cough, fever and weight loss. According to several studies, in diabetic patients prevalence of haemoptysis is higher and prevalence of dyspnea and loss of appetite is higher in non diabetic patients [19]. Large number of smear positive results in TB patients with DM in comparison with patients of TB without DM was observed. According to a study also risk of relapse in TB patients with DM shows increase of four fold versus TB without DM [30]. Former study on TB patients of southern Texas and northern Mexico shows that in diabetic patients, production of IFN-γ, IL-2, TNF-α, and GM-CSF is higher than non diabetic TB patients as shown in **Figure 2** [25].

Can we reduce tuberculosis by targeting diabetes?

DM can hamper the treatment of TB. We can decrease the mortality rate through TB by preventing diabetes. If diabetes continues to increase at current rate, it will tedious to prevent TB. We can say if we target diabetes as one of the associated factors of TB, it will optimize treatment response of TB [22]. According to journal of Diabetes and metabolism, it is discovered that if beta cells are treated with vitamin D or derivative of vitamin D (eg. LCA propionate) it can protect the function of beta cells by enhancing the expression of genes which encodes insulin [37]. Thus we can conclude that it will prevent or cure diabetes and through this mechanism, we can indirectly reduce TB because vitamin D deficiency is also one of the associated factors with higher risk of TB. Individuals, who are vitamin D deficient, also have susceptibility to develop TB and also disease progression get worsen in these individual if infected with TB. Anti mycobacterial activity is also promoted by vitamin D supplement [38]. Vitamin D treatment inhibits mycobacterial entry and also restricts its survival within macrophage. Therefore it could predict that, the burden of this co infection of TB and DM could be managed simultaneously through supplement of vitamin D [39,40].

Table 1 T-cell response in TB patients with diabetes and without diabetes.

S. No.	Criteria	TB in diabetic patients	TB in non-diabetic patients	References
1.	T-cell response	Quantitatively -greater	Quantitatively-lesser	[26]
		Functionally - less effective	Functionally- more effective	
2.	Common symptoms	Cough	Cough	[19]
		Fever	Fever	
		Loss of appetite	Weight loss	
3.	Risk relapse	4-fold increase	Lesser chance	[30]

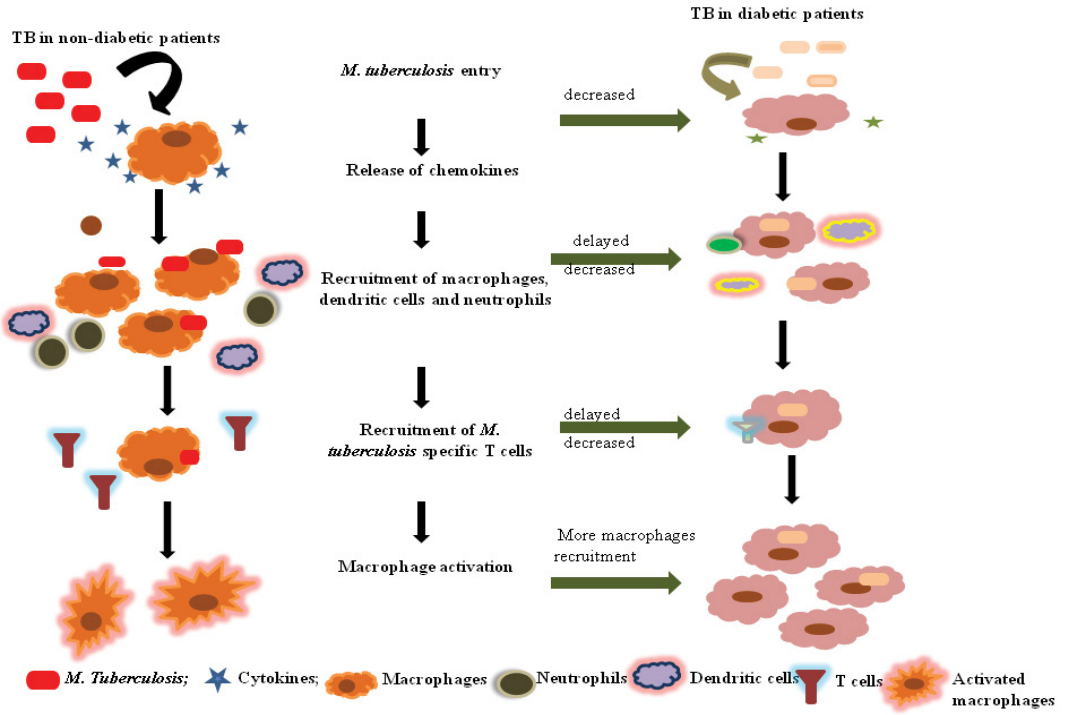

Figure 2 Immunological insight comparison of a diabetic and non diabetic individual-This figure shows a dysfunctional immune response results in delayed adaptive immunity in case of tuberculosis in diabetes patient. At first alveolar macrophages become infected with *M. tuberculosis*. Alveolar macrophages are unable to inhibit *M. tuberculosis* replication but in case of diabetic patients, lower the production of chemokines and delayed the recruitment of neutrophill and dendritic cells due to which individual become more prone to infection. Due to this delay delivery of antigen is also delayed and the subsequent expression of adaptive immunity during the long period of *M. tuberculosis* replication. This scenario increases the severity of pathology and worsens the outcomes of this co-relation.

Conclusion

Rare co relation between communicable and non communicable diseases such as the one seen in Tuberculosis and diabetes has created problems in treating both simultaneously. This association is the next challenge for controlling global burden of tuberculosis. Some Novel therapeutic approaches should be designed which can target the hindrance created by diabetes in the treatment of TB, as immune cell in diabetic individual show less efficiency to kill *M. tuberculosis.* Hence, designing new drug pipelines that can target TB and diabetes simultaneously is vital so that we can enhance the interaction between macrophages and *M. tuberculosis.* If it is possible to deal with immune compromise stage of diabetes then we can cure or prevent TB lead by diabetes. Cross-sectional imaging methods, for example, CT and MR imaging, depend on morphologic criteria for the evaluation of pneumonic and mediastinal tumors [41-43]. Addressing co-relation between DM and *M. tuberculosis* transmission is crucial to achieve control of these diseases in high burden cities. Repeated surveys measuring tuberculosis infection in diabetic patients in the same community involving young individuals can give us an estimate of tuberculosis transmission. This strategy can be used in high burden urban areas to calculate transmission of tuberculosis and develop strategies to reduce its progression. Priority should be given to the development of health assessments to eradicate diabetes from population to achieve support in TB prevention stratagem.

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