



Clinical significance of the levels of HbA1C and vitamin D & B12 in tuberculosis patients with diabetes

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Abstract

There have been studies on establishing association between Vit D status and insulin secretion and insulin sensitivity with differing results in various ethnic populations. Many have studied the effect of Vit D supplementation on T2DM again with differing results. With Vitamin D deficiency prevailing in epidemic proportions all over the Indian subcontinent and with a phenomenal prevalence of 70%–100% in the general population, we thought it was important to elucidate the status of vitamin D and its possible relation with insulin resistance in Type 2 DM. Hence based on the above reported findings the present study was planned to study clinical significance of the levels of hba1c and vitamin D & B12 in tuberculosis patients with diabetes.

The present study was planned in Narayan Medical College and Hospital, Jamuhar Sasaram, Bihar, India. Total 100 patients referred to Department of General Medicine were enrolled in the present study. The 50 cases of the diabetes diagnosed with the tuberculosis were evaluated as cases and 50 cases of the normal cases were evaluated as a control cases. Serum levels of vitamin B-12 were measured by electrochemi-luminescence immunoassay. Levels of 25-hydroxy vitamin D3 [25(OH) D3] were measured by radioimmunoassay (RIA). Levels of HbA1c were measured by high-performance liquid chromatography (HPLC). Blood pressure, height, body weight, and waist and hip circumferences of each patient were measured as an anthropometric and dietary measurement. Body mass index (BMI) and ratios of waist to hip circumference was calculated. Blood pressure of each patient was measured after giving rest for at least 5 min.

The data generated from the present study concludes that the levels of the HbA1C were increases in Diabetes patients with TB whereas the levels of the Vitamin D and Vitamin B12 were decreases in diabetic patients with TB.

Keywords: Diabetes (DM), Tuberculosis (TB), HbA1C, Vitamin D, Vitamin B 12, etc

1. Introduction

Diabetes is a chronic (long-lasting) disease that affects how the body turns food into energy. Tuberculosis (TB) is a serious health threat, especially for people living with diabetes. Two TB-related conditions exist: latent TB infection and TB disease. People with latent TB infection are not sick because the body is able to fight the bacteria to stop them from growing. People with TB disease are sick and have active TB because the body cannot stop the bacteria from growing. People living with diabetes who are also infected with TB are more likely to develop TB disease and become sick with TB. Someone with untreated latent TB infection and diabetes is more likely to develop TB disease than someone without diabetes. Without proper treatment, diabetes and TB can increase health complications. Untreated latent TB infection can progress to TB disease. TB disease, without treatment, can progress from sickness to death. Fortunately, treatment options are available for people with diabetes who also have either latent TB infection or TB disease. If a person is diagnosed with TB infection, further testing is required to rule out TB disease. People with either latent TB infection or TB disease can be effectively treated. Before beginning treatment for TB disease or for latent TB infection, TB patients should talk to their doctor about any other medication they are taking, including medicine for diabetes. Some medications used to treat TB might interact with medicine used treat diabetes [1].

Patients with DM are not only at a higher risk of TB, but may face worse treatment outcomes. The success of a TB treatment can be evaluated with several end points: interim

results of sputum culture conversion after 2–3 months of treatment, which is correlated with treatment success [2-3]; cure or failure rate at the end of treatment (typically 6 months for standard therapy); death rate within the treatment period; and rate of relapsed or recurrent TB among those who successfully completed treatment. A recent meta-analysis summarized studies that have investigated the association between DM and several outcomes of TB treatment, including culture results at 2–3 months of treatment, treatment failure, and death and relapse of TB. Nine studies investigated the impact of DM on positive sputum culture 2–3 months after the beginning of treatment. While five of these studies showed that DM patients were two-to three-fold more likely to have culture-positive TB after 2–3 months, other studies demonstrated no impact. The significant heterogeneity between the studies ($I^2 = 58\%$) may be due to variability in control or lack of control for confounding factors, differences in the severity of DM among some studies, and heterogeneity in the effect of DM on TB disease. Studies that considered the impact of diabetes on the combined outcome of failure or death showed that DM patients were approximately 1.7-times more likely to fail treatment or die during treatment. Studies that examined death as the sole outcome showed a similar increased risk of death (relative risk [RR]: 1.89). What is more, studies that optimally controlled for potential confounders, such as age and other comorbidities, found an even greater risk of death among those with DM (RR: 4.95). The systematic review also identified five studies that showed that patients with DM were more likely to experience relapse TB (RR: 3.89); however, there was no

clear association between drug resistance and DM among those with recurrent TB ^[4].

TB patients with DM may face worse outcomes than those without DM for several reasons. First, as evidenced in *in vivo* and *in vitro* studies, DM affects the innate and adaptive immune responses necessary to control TB infection ^[5]. Second, while reduced ability to clear infection could conceivably lead to TB-related deaths among people with DM specifically, it is also possible that these patients face a greater likelihood of death during TB therapy because of DM-associated complications, such as heart disease, stroke and renal failure. Unfortunately, the studies discussed above did not attribute the deaths to specific causes. Third, DM may affect the pharmacokinetics of TB drugs so that the bactericidal activity is lessened. One study by Nijland *et al.* demonstrated that in Indonesian patients with DM, maximum rifampicin concentration in serum was markedly lower during the continuation phase of treatment compared with that of patients without DM ^[6], although a more recent study did not find that the pharmacokinetic properties of rifampin, pyrazinamide and ethambutol were different among patients with diabetes during the intensive phase of TB treatment ^[7]. Some patients with DM may have renal failure that requires fine-tuning of dose or interval of administration owing to potential toxicity by accumulation of drugs or potential dilution through hemodialysis ^[8]. Furthermore, the administration of rifampicin may interfere with pharmacokinetics of hypoglycemic agents, such as glyburide and rosiglitazone, which impedes glucose control ^[9-10]. These pharmacodynamic interactions may all contribute to poorer outcome among TB patients with DM. Finally, patients with DM may face a higher chance of recurrent TB due to reduced immunity that increases the vulnerability to reactivation of the prior infection ^[11].

While these data suggest that people with DM are more likely to face treatment failure, death and relapse, there is little evidence for an association between glucose control and TB treatment outcomes. A study by Chang *et al.* examined how TB outcomes varied according to glucose control and duration of DM, but did not find that treatment failure was associated either with longer duration of DM or baseline hemoglobin A1C levels, a marker of long-term glucose control ^[12]. However, the study was limited by power; only 60 patients with DM were included among 192 patients in the analysis of treatment failure. A clear understanding of the effects of glucose control on TB treatment outcomes is an important piece of the puzzle in determining whether good glucose control could help to reduce bacterial burden, leading to better cure rates and lower mortality.

Given the association between DM and TB treatment outcomes, experts have made both clinical and operational recommendations to try to improve the outcomes of TB patients with DM. Optimal management of DM-associated TB begins with early case detection before advanced progression of TB and the prevention of transmission through infection control. To this end, the WHO Collaborative Framework for Care and Control of Tuberculosis and Diabetes recommends that healthcare providers of patients with DM remain alert to potential TB symptoms and implement appropriate infection control measures at DM clinics ^[13].

Testing for latent TB infection (LTBI) in people diagnosed with DM to identify those eligible for TB preventive therapy

may also be an effective way to reduce future burden of incident TB ^[14]. Patients with DM with poor glycemic control (i.e., >7% hemoglobin A1C), in particular, are important targets for LTBI testing, given that they are more likely to develop TB compared with those without diabetes. A previous study conducted in the 1960s in Russia showed that 5 years of administration of chemoprophylaxis with an isoniazid analog, ftivazid, reduced the risk of primary TB in patients with DM twofold compared with the risk in those who received 1 year of chemoprophylaxis ^[15], but we are aware of no recent studies that report on the efficacy of currently recommended regimens of TB preventive therapy. Regardless, given the increased risk of TB among those with poorly controlled diabetes and the benefit of TB preventive therapy, patients with diabetes with LTBI should be offered preventive treatment according to the guidelines set forth by the American Thoracic Society ^[16]. The optimal frequency of testing for LTBI depends on the background TB incidence rate and the host factors that influence risk of reactivation and is therefore specific to local practice and the clinical profile of individuals with DM ^[14].

TB programs should also be encouraged to screen for DM among TB patients and help facilitate high-quality DM management ^[13]. Specifically, experts recommend screening for high glucose levels in TB patients by fasting blood glucose, random blood glucose or hemoglobin A1C. Repeat testing of glucose levels in the first 4 weeks of TB treatment in those who initially present with high glucose levels would help confirm DM status and identify patients in need of oral diabetic medications or insulin. This necessitates point-of-care glucometers in TB clinics and training TB healthcare workers to interpret and follow up on the results of the glucose testing ^[14]. TB control programs in the Pacific, including Pohnpei where DM prevalence reaches 32% according to WHO STEPS chronic disease risk factor surveillance ^[16], have begun monitoring glucose levels in newly diagnosed TB patients, finding an alarmingly high prevalence of DM (>50%), with high hemoglobin A1C levels reaching beyond 10% in a number of patients [Brostrom R, Pers. Comm.]. Similar efforts to screen glucose levels in TB patients have started in India and in China ^[17] where the number of people with DM is rapidly increasing. TB programs should also consult current standards for medical care for people with DM that recommend target capillary plasma glucose levels (70–130 mg/dl for preprandial and <180 mg/dl for peak postprandial) and hemoglobin A1C levels (<7.0%), and set forth guidelines on pharmacological, dietary and lifestyle interventions ^[18]. The standards also provide guidelines for prevention and management of diabetes complications in critical and noncritical settings.

In addition to screening for DM, the Pacific Islands TB Controllers Association recommends providing DM education to TB patients with DM, which includes guidelines for changes in diet and physical activity that synergistically improve glucose control ^[37]. A few experts also advocate the use of directly observed therapy in administering DM medications to those with poorly controlled DM as a way to extend existing TB resources to DM management. A study is underway in the US-affiliated Pacific Islands that aims to examine the ability of TB programs to follow patients for both TB outcomes and glucose control. The study will also evaluate whether healthcare workers devoted to directly observed therapy

could document control of DM and deliver DM education. Such feasibility studies are crucial in determining the combination of interventions that could be successfully implemented in the field [19].

Altered pharmacokinetic dynamics of TB medications in patients with DM may warrant adjustments in the TB treatment regimen. Pyrazinamide and ethambutol doses, in particular, may need to be adjusted based on creatinine levels in patients with diabetic nephropathy. In this regard, Gnanasan et al. recommend that pharmacists could play a role in ensuring adherence and providing individualized pharmaceutical care management to TB patients with DM [20]. Pharmacists may also help to prevent adverse events due to toxicity or drug–drug interactions and may be more available in the community than physicians to monitor such conditions.

India has been called “the Diabetes capital of the world,” and it is estimated that 41 million Indians have the disease and “every fifth diabetic in the world is an Indian.2 Although there are now improved treatments available for treating the disease and its complications, prevention would always be preferable for this multisystem disorder which is one of the leading causes of mortality and morbidity. An interesting angle to the etiopathogenesis of Diabetes which is being studied, is the role of Vitamin D insufficiency as a risk factor, which may play a role in development of both type 1 and type 2 Diabetes Mellitus [21-22].

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Methodology

The present study was planned in Narayan Medical College and Hospital, Jamuhar Sasaram, Bihar, India. Total 100 patients referred to Department of General Medicine were enrolled in the present study. The 50 cases of the diabetes diagnosed with the tuberculosis were evaluated as cases and 50 cases of the normal cases were evaluated as a control cases. Serum levels of vitamin B-12 were measured by electrochemi-luminescence immunoassay. Levels of 25-hydroxy vitamin D3 [25(OH) D3] were measured by radioimmunoassay (RIA). Levels of HbA1c were measured by high-performance liquid chromatography (HPLC). Blood

pressure, height, body weight, and waist and hip circumferences of each patient were measured as an anthropometric and dietary measurement. Body mass index (BMI) and ratios of waist to hip circumference was calculated. Blood pressure of each patient was measured after giving rest for at least 5 min.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

In 2011, understanding the severity of the co-epidemics of TB and DM, with the absence of national guidelines on joint management and to control the co-epidemics, the World Health Organization (WHO) along with International Union Against Tuberculosis and Lung Disease (The Union) launched a collaborative framework for care and control of TB and DM. The aim of the framework was to guide national programmes, clinicians and other individuals associated with prevention and control of DM and TB. This framework is only provisional and revisions are to be made in order to fill the gaps between the knowledge of DM and TB co-epidemics. However, despite the guidelines having been released, several challenges are being faced by countries like India and China, which record the highest load of TB and DM. There are numerous studies from different regions of the world supporting the association of DM and TB. DM patients with TB have worse treatment outcomes, case fatality and treatment failure. There is some evidence to suggest that TB in diabetic patients may have different clinical manifestation. DM increases the risk of poor treatment outcomes in TB patients. Strict glycaemic control may achieve better treatment outcomes.

Experimentally vit D is required for normal insulin secretion and glucose tolerance.5 Inadequate calcium intake or vitamin D insufficiency may alter the balance between the extracellular and intracellular β -cell calcium pools, which may interfere with normal insulin release. It is proposed that Vitamin D is an important risk factor in development of insulin resistance and the pathogenesis of type 2 DM by affecting either β-cell function, through the presence of vitamin D receptors on the beta cells or through the effect on calcium metabolism, or both [25]. Also, Vitamin D improves insulin sensitivity by its anti-inflammatory activity as it is proposed to attenuate the expression of pro-inflammatory cytokines involved in insulin resistance [26-27].

Table 1: Age group and No. of cases

	Case Group	Control Group
Group of	Diabetes with TB	Normal Cases
No. of Cases	50	50
Age in Years		
20 – 30 years	3	4
31 – 40 years	8	6
41 – 50 years	14	15
51 – 60 years	12	17
60 and above years	13	8
Total	50	50

Table 2: Levels of Vitamins and HbA1C+

Group of	Case Group	Control Group
	Diabetes with TB	Normal Cases
No. of Cases	50	50
HbA1C (%)	7.5 – 8.7	4.4 – 5.9
Vit B12 (pmol/L)	174.5 – 257.6	321.8 – 378.5
Vit D (ng/ml)	15.34 – 19.68	18.48 – 26.23
BMI	25.4 – 31.7	21.4 – 27.6

Among patients afflicted with both TB and DM, diabetes is reported to be associated with poor TB treatment outcomes [28]; however, a systematic analysis to clarify and quantify the association between DM and TB outcomes, including persistence of sputum culture positivity, treatment failure, death and relapse, has not been performed [31]. This systematic review of the effect of DM on TB treatment outcomes has determined that DM increases the risk of death reported to be 6.5–6.7 times higher in TB patients with DM. The question of TB preventive therapy may only be answered with a randomized controlled trial, an expensive and difficult way to conduct proposal. A study from Kerala, India showed that non-drug resistant TB patients with DM were more likely to fail first-line TB treatment when compared with patients without DM.[29] Screening and attention to better DM control might be a more cost-effective way of preventing TB and reducing other DM complications [30].

The meta-analysis conducted by Anastassios G. Pittas et al concluded that calcium and vit D levels had negative influence on glycemia [32]. They searched MEDLINE for observational studies on the association between vitamin D / calcium status and T2DM (prevalence or incidence) and for randomized controlled trials of the effect of vitamin D and/or calcium supplementation in non-pregnant adults on outcomes related to glycemic control. There is a growing evidence that Vitamin-D levels are inversely associated with development of diabetes independent of risk factors like age BMI and race. The NHANES data confirmed the inverse relationship between 25(OH)D levels and diabetes and insulin resistance in the non-Hispanic white and Mexican American, but not in the non-Hispanic black populations [33-34].

Faurholt-Jepsen et al., [35] in a prospective cohort study of the same study population also demonstrated that DM is a strong predictor of early mortality during anti TB treatment. In the initial 100 days, diabetes was associated with a fivefold increased risk of mortality [relative ratio (RR): 5.09, 95% CI: 2.36-11.02, $P < 0.001$] among HIV uninfected, and a twofold increase among HIV co-infected patients (RR: 2.33 95% CI: 1.20-4.53, $P = 0.012$). However, it was not associated with long-term mortality.

A study in Ethiopia resulted in prevalence of smear positive Pulmonary TB was 6.2% in TB suspected diabetic patients, which is higher compared with the general population (0.39%). It was also found that Patients with a previous history of contact with TB patients, as well as those who had prolonged diabetes, were more prone to have PTB. [36] A retrospective study in Texas and Mexico found 27.8% of Texan and 17.8% of Mexican TB patients suffered from Diabetes. It has been reported that patients with TB and diabetes were more likely to be smear positive at diagnosis, and remain positive at the end of the first or second month of treatment [37].

The levels of leptin were significantly higher in TB patients than TB+T2DM. The level of ghrelin was significantly lower in TB and insignificantly lower in TB+T2DM. Possible abnormalities in leptin and ghrelin regulation may be associated with the development of poor nutrition (low BMI) during the inflammatory response in TB patients with or without T2DM. TB patients with T2DM may have more complex and different pathogenesis compared to TB patients only. In our study TB-DM patients who had undergone HbA1c test had poor glycemic control. In India tuberculosis and diabetes mellitus study shows that higher rates of DM were found among patients with a known history of TB [38].

While the association of diabetes mellitus and tuberculosis poses a serious challenge to our efforts to control both diseases, the coexistence of these two conditions also provides a huge public health opportunity. Strategies for early detection of diabetes and tuberculosis when they coexist with each other will be critical in controlling the rising prevalence and impact of both. National guidelines for bi-directional screening of diabetes mellitus and tuberculosis when patients present with either of these two conditions is a welcome step in this direction. There is also a need to undertake further studies particularly cohort studies to unravel some of the missing links in the coexistence of diabetes mellitus and tuberculosis. More importantly, there is an urgent need to develop clinical practice recommendations for diagnosis, prevention, and control of diabetes mellitus–tuberculosis to facilitate a uniform and effective approach that will help contain this twin problem.

Conclusion

The data generated from the present study concludes that the levels of the HbA1C were increases in Diabetes patients with TB whereas the levels of the Vitamin D and Vitamin B12 were decreases in diabetic patients with TB.

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