ORIGINAL ARTICLE

Effect of Glycemic Control on Radiological Manifestations of Pulmonary Tuberculosis –A Hospital Based Study

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ABSTRACT

Objectives:

- To study the frequency of diabetes in patients with active pulmonary tuberculosis.
- To determine the impact of diabetes on radiological findings in tuberculosis.
- To study the association of atypical radiological manifestations with glycemic control in diabetes associated tuberculosis.

Study Design: A Descriptive study.

Place and Duration of Study: The study was conducted in Medical Department of Pakistan Air Force Hospital Mianwali from August 2013 to July 2014.

Materials and Methods: Seventy five new cases (18 years and above) of active pulmonary tuberculosis were selected by non-consecutive convenient sampling. All patients received standard anti-tuberculous treatment (ATT) for six months. Fasting blood glucose and chest X-ray were performed in all patients. Glycosylated hemoglobin (HbA1c levels) were checked to assess the glycemic control in diabetic patients. Radiographic features of the two groups; diabetic vs. non diabetic and within diabetic population; poor vs. optimal glycemic control, were then compared.

Results: Thirty three (33/75 or 44%) patients were found to be diabetic. Radiological changes were more frequently atypical in diabetic group as compared to non diabetic population (21/33 or 63.6% vs. 8/42 or 19%). Nine of the 12 diabetic patients with poor glycemic control i.e. HbA1c levels >7% had cavitations, lower zone involvement and bilateral changes as compared to 11/21 patients with optimal glucose control i.e. HbA1c <7% and the difference was significant (9/12 or75% vs.11 /21 or 52.3%, p value <0.001).

Conclusion: A high index of suspicion for diagnosis of diabetes is required for TB patients with atypical radiological manifestations. Poor glycemic control is related with atypical findings on chest X-ray in pulmonary tuberculosis.

Key Words: *Atypical Chest X-Ray, Diabetes, Glycemic Control, Pulmonary Tuberculosis.*

Introduction

The re-emerging global pandemics of type 2 diabetes mellitus (DM) and tuberculosis (TB) is a serious threat to the attainment of Millennium Development Goals (MDG's) for Tuberculosis especially in the low and middle income countries of the world.[1] The looming co-epidemic of tuberculosis-diabetes (TB-DM) in South Asia is being compared to the tuberculosis- human immunodeficiency virus (TB-HIV) co-epidemic of sub-Saharan Africa in 80's and 90's, as one disease seems to fuel the other in the same manner.[2] A recent study on association between tuberculosis and diabetes in the developing region of Africa has shown that countries with rising diabetes prevalence have depicted a simultaneous increase in the prevalence of tuberculosis.[3] There is now sufficient evidence to suggest that TB patients with diabetes are more likely to experience an aggressive course of disease with more chances of treatment failure, multi-drug resistant TB (MDR-TB), relapse and death.[4] Literature review reveals that diabetes frequently alters the radiological manifestations of pulmonary tuberculosis.[5] Atypical findings are common with lower zone involvement, cavitations, multiple and/or bilateral lesions which are often misdiagnosed as pneumonia, lung abscess etc with delay in treatment. Recently it has also been suggested that poor glycemic control may be linked to atypical radiological findings in such patients.[6]

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Funding Source: NIL ; Conflict of Interest: NIL
Received: Feb 16, 2016; Revised: Apr 07, 2016;
Accepted: May 09, 2016

Despite such conclusive evidence, unfortunately no separate guidelines/protocols for treatment of tuberculosis patients with diabetes currently exist. World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease in 2011 issued a global recommendation of bidirectional screening for early detection and management of both diseases.[7] Countries like China and India have already incorporated these recommendations into their TB-DM screening programs. However, in Pakistan, a country with one of the highest figures for both tuberculosis and diabetes, serious gaps between recommendations (including National TB Guidelines) and current practices still exist.

Present study was conducted to highlight the association of TB and DM and to investigate the impact of glycemic control on radiological manifestations of patients with coexistent TB and DM in our hospital setting. Published data on this association is still scarce. To our knowledge, no such study has been conducted in Pakistan so far.

Materials and Methods

This descriptive study was conducted in the Medical Department of Pakistan Air Force Hospital Mianwali from August 2013 to July 2014. The study was initiated after the approval of study proposal by the Hospital Ethics Committee after incorporating its suggestions to protect the patient's confidentiality. Seventy five new cases (18 years and above) of active pulmonary tuberculosis were selected by non consecutive convenient sampling after informed consent. Exclusion criteria included relapse cases, patients with extra pulmonary TB, type 1 diabetes, impaired fasting glucose, pregnancy and endocrinological disorders. Patients with immunocompromised states/comorbids such as HIV, chronic renal failure, cirrhosis or malignancies that could cause possible stress hyperglycemia and hence act as confounders were not included. Similarly patients taking drugs known to cause hyperglycemia such as steroids, beta agonists and thiazide diuretics were also excluded from the study. Active pulmonary TB was diagnosed when a patient with clinical features of TB met at least one of the following three criteria; a positive sputum smear, a positive sputum culture, or a positive chest radiograph.[8] Patients were divided into two groups; diabetes-associated TB patients (DMTB group) and non diabetic TB only patients (TB-only group). All patients received 4 drugs standard ATT in the initiation phase and 2 drugs in the continuation phase and treatment was monitored by parameters defined by the National TB guidelines.[8] Screening for diabetes mellitus was done by twice measured fasting blood glucose levels. Diagnostic criteria for diabetes followed the WHO guidelines; > 126 mg/dl fasting plasma glucose.[9] ATT transiently elevates glucose levels, therefore samples for blood glucose were taken before beginning ATT and repeated at 12 weeks. HbA1c levels were performed in all diabetic patients (previously known or newly diagnosed on screening) to determine the level of glycemic control. DMTB patients were then further subdivided into two groups. Patients with HbA1c levels > 7% were considered as having poorly controlled diabetes while patients with HbA1c < 7% had optimal glycemic control.[10] Chest X-ray findings that were considered atypical included lower zone involvement, bilateral involvement, large cavities (>2cm) and/ or multiple cavitations.[5,11] Radiographic features of the two groups with poor and optimal glycemic control were then compared.

Data was analyzed using IBM SPSS 20. Categorical data was calculated as frequencies and percentages. Mean and standard deviation was calculated for age. The chi-square test was used to test the statistical significance of categorical variables such as HbA1c levels and atypical chest X-ray and p-value of less than 0.05 was considered significant at 95% confidence interval.

Results

There were 35 male and 40 female patients. Only 6% were below 40 years of age while 26% patients were 70 years or older. Out of 75 new cases of pulmonary tuberculosis, 33 (44%) were found to be diabetic and constituted the TBDM group while 42/75 (56%) were non diabetic and constituted TB-only group. In the TBDM group, 20/33 (60.6%) were known diabetics and 13/33 (39.3%) were newly diagnosed detected on screening. Poorly controlled diabetes (HbA1c >7%) was observed in 12/33 (36.3%) diabetic patients and required insulin for sugar control. In 21/33 (63.6%) patients, HbA1c was < 7% and glycemic control was achieved with oral hypoglycemic agents. In none of the 33 diabetic

patients blood sugar was controlled with diet alone. Radiological changes were more frequently atypical in DMTB group as compared to TB-only group (21/33 or 63.6% vs. 8/42 or 19%). (Table I).

Table I: Frequency of atypical chest X-ray in diabetic and non-diabetic TB Patients (n=75)

Diabetes Status	No. of TB Patients	AtypicaL CXR	Percentage
Diabetic	33	21	21/33 (63.6%)
Non Diabetic	42	8	8/42 (19%)
Total Number	75	29	-

The presence of atypical changes was associated with poor glycemic control and insulin use. Nine of the 12 diabetic patients with poor glycemic control (HbA1c levels >7%) had cavitations, lower zone involvement and/or bilateral changes as compared to 11/21 patients with optimal glucose control (HbA1c <7%), (Table II). The difference was statistically significant (9/12 or75% vs.11 /21 or 52.3%, p value<0.001).

Table II: Atypical chest X-ray in TB patients with poor glycemic control

Diabetes Control	Typical CXR	Atypical CXR	Total Diabetic Patients	% With Atypical CXR
Hb A1c <7% (optimal)	10	11	21	11/21 (52.3%)
HbA1c >7% (poor)	3	9	12	9/12 (75%)
-	-	-	33	-

Discussion

In our study, 63.6% of patients in TBDM group were seen to have atypical radiological manifestations as compared to 19% patients in the TB-only group. Glycemic control is an important aspect of TB management and may have an effect on radiological manifestations. An attempt was thus made to correlate the two in the present study. Interestingly, a significant association existed between atypical radiological manifestations and poor glycemic control as DMTB patients with HbA1C levels >7% were more likely to have lower zone involvement, cavitations and/or bilateral changes as compared to non diabetic TB patients (76.9% vs. 55%, p value <0.001).

Literature review reveals that screening for DM in TB patients yields high prevalence of DM ranging from 1.9% to 35% depending on the geographical location.[12] In the present study, 44% of TB patients had co existing DM, a rate more than thrice the prevalence of diabetes in Pakistan (12.1% in males and 9.8% in females).[13] The frequency of newly diagnosed diabetes was 39.3% in our study which is also higher than most previous studies[14,15,16]and highlights the significance of screening for diabetes in all patients with tuberculosis.

Pulmonary TB has a propensity to affect upper lobes of the lungs. It is still a matter of debate whether or not the presence of diabetes alters the radiological manifestations of PTB.[5,17] Previously authors have reported that chest X ray findings are frequently atypical in TB patients having diabetes; with lower zone involvement, cavitations, bilateral changes and multi lobe involvement.[18,5] The study by Parez-Guzmann was most striking in this aspect who determined that diabetes was the most significant factor in development of lower lung lesions.[5] In one of the more recent studies conducted, Patel et al also reported a high frequency of atypical chest X-rays in patients with coexistent TB and DM.[19] However other authors do not report any significant difference.[17]

Literature search revealed that data regarding association of radiological manifestations with glycemic control is scarce. Earlier, Park et al suggested that poor glycemic control was linked to a higher incidence of cavitatory lesions.[18] In a recently conducted Indian study, Avathu et al studied 70 diabetic patients with PTB and concluded that atypical changes were more frequently seen in diabetic patients with HbA1c levels >7% and poor glycemic control as compared to those with optimal control.[10]A most recent large scale study conducted in Taiwan also reported significant correlation between poor glycemic control and atypical radiological features.[6] The findings of the present study are thus in agreement with these few studies.

Tuberculosis was a deadly threat to diabetic patients

in the pre-insulin era. Poor diabetes control possibly exacerbated by co-existent tuberculosis affects innate cytokine responses. Suboptimal glycemic control not only predisposes to tuberculosis, it often leads to poor ATT response. This could result in higher chances of complications with treatment failure, relapse and case fatality. Anti tuberculous drugs and oral hypoglycemic agents have complex interactions with one another and diabetes patients may have lower concentrations of anti-TB drugs.[2] While drugs such as rifampicin are known to cause transient hyperglycemia, some of the newer oral hypoglycemic agents such as gliptins can lower the efficacy of ATT. Resultant TB associated hyperglycemia often worsens the glycemic control of diabetes necessitating timely switching to insulin.[20] In the present study, 36.3% of the patients with TB had uncontrolled hyperglycemia (HbA1c >7%), and required insulin for sugar control. Although we did not have a comparison group of diabetes-only patients, it is noteworthy that in none of the TBDM patients blood sugar could be controlled with diet alone. A significant number of newly diagnosed diabetics also had poorly controlled diabetes.

Previously, a similar study from Lahore (Pakistan) had determined the frequency of diabetes in TB patients as 25.9% and that of the newly diagnosed cases as 5.69%.[14] Balakrishnan et al have reported the frequency DM in TB as 44% in India, a country with similar demographic and socioeconomic background.[15] The incidence of newly diagnosed diabetes cases in their study was 21%.

PAF Hospital Mianwali is one of the peripheral hospitals in Mianwali District catering for the needs of all the patients affiliated with Pakistan Armed Forces from District Mianwali, Chakwal, Khushab, DI Khan, Layyah and Bhakkar. Moreover it has a high turnover of civilian patients. The limitations of our study include a relatively small sample size due to limitation of resources and a high number of patients being lost to follow up by virtue of peripheral location of our hospital. In addition we also applied stringent exclusion criteria such as exclusion of patients with impaired fasting glucose and including only patients who were followed up until complete duration of treatment. Despite these limitations, our study not only augments previous local studies in terms of a high occurrence of DM in patients with pulmonary TB, it also highlights other clinical aspects such as maintaining strict glycemic control with frequent monitoring and possible switching to insulin, when treating TB patients with coexisting DM. Further large scale studies from other regions of Pakistan are needed to explore these aspects in detail. Similarly standards and protocols have to be developed at hospitals and national level for diagnosis and treatment strategies for management of diabetes mellitus in newly diagnosed cases of tuberculosis.

Conclusion

We conclude that optimal glycemic control is an integral component of TB treatment. A high index of suspicion for diabetes is required for TB patients with atypical radiological manifestations. Active screening for diabetes in all patients with tuberculosis can be a more cost-effective way of controlling and preventing both diabetes and tuberculosis.

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