REVIEW ARTICLE

Tuberculosis & Diabetes Mellitus – Impact of Co- Association

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Abstract: -

Tuberculosis (TB) & Diabetes Mellitus (DM) are common diseases in Pakistan & both are on rising trend, so not surprisingly they co-exit. Patient with diabetes mellitus are susceptible to infections & tuberculosis is one of them. For people with tuberculosis infection & having diabetes mellitus the risk to develop disease is as high as three times and up to 30% over a life time as compared to non diabetic patient with the TB infection. The problem of TB patients' management with diabetes is compounded by delay in diagnosis as both disease share symptoms such as lassitude, weight loss & anorexia etc. The possibility of concomitant diabetes should be considered in patient with poor clinical response to Anti tuberculous drugs/ treatment (ATT) & similarly the suspicion of associated TB infection should be considered in patient with uncontrolled diabetes.

Key Words: -
Tuberculosis, Diabetes mellitus, infection, Pakistan ,

Tuberculosis & Diabetes Mellitus – Impact of Co-Association

Introduction:

Tuberculosis (TB) & the Diabetes Mellitus (DM) are common disorders & not surprisingly they co-exit. The co-association has been observed for more then 2000 years. Avicenna (780-1027AD) had commented that phthisis frequently complicates diabetes.[1] Before the discovery of insulin the diagnosis of diabetes was death sentence within five year and the usual cause of

death was tuberculosis.[2] TB occurs with an increased frequency in diabetics and at the same time TB appears to aggravate diabetes, with patients requiring higher doses of insulin/oral hypoglycemic agents to achieve glycemic control. With the advent of effective ATT and hypoglycemic agents, the prognosis of pulmonary tuberculosis complicated by diabetes is not as grave as it was in the past. However, numerous difficulties still exits in the diagnosis and management of this grave association. In this review, we will describe impact of association of two diseases clinically with the background that both diseases have a rising trend in Pakistan .

Tuberculosis & Diabetes Mellitus:

Diabetic patients are not only susceptible to infections, but when infections occur they are more severe as diabetic patient is a compromised host. DM is also recognized as an independent risk factor for lower respiratory tract infection.[3] Whereas infection with *staphylococcus aureus*, gram negative bacteria, and fungi occur more frequently in diabetics, organisms like *streptococcus, legionella and H. influenza* cause significantly higher morbidity and mortality in diabetics.[4] The global prevalance of diabetes is projected to rise from the current estimate of 150million to 200million in 2010 and to 300million (5.4%) in 2025.[5] The potential for increase in the number of cases of diabetes is greatest in Asia. It is an emerging public health problem of significant proportion.

In Pakistan , Diabetes is assuming serious proportion with 12% of its inhabitants above 25 years suffering from this condition and another 10% having impaired glucose tolerance. Diabetes effects roughly 4 to 5 millions people in Pakistan.[6] In a survey which was conducted in province of Sindh , it was concluded that the prevalence of diabetes had risen with age to peak of 30% and 21% in 65 – 74 years old men and women respectively.[7]

Regarding TB, Pakistan ranks 6th among the 22 countries with highest burden and contributes about 44% of TB burden in Eastern Mediterranean region of WHO.[8] Calculated incidence of

TB in Pakistan is 181 per 100,000 population per year, and prevalence of 297 cases per 100,000 population. Incidence of new AFB smear positive cases is 82 per 100,000 population per year. Primary multi drug resistant tuberculosis (MDR–TB) is reported up to 1.9 %. TB mortality is 37 per 100,000 per year.[8]

The link between DM and pulmonary TB has been discussed & published in the world literature, but has never received the attention it deserves. Patients with DM are at a high risk of TB, and this has been highlighted by several retrospective and prospective studies [5,9,10]. In a large Cohort study of over eight thousands Indian patients with DM, TB was found to be the most complicating illness with incidence of 5.9%.[11] While another study published in 2002 from India showed prevalence of pulmonary TB of up to 27% in diabetic patients by radiological diagnosis and 6% by sputum positivity[9]. For people with TB infection and no risk factors, the risk to develop Tuberculosis disease is 5% in first 2 year, and up to 10% over a life time. For people with TB infection and Diabetes the risk is 3 times high and is up to 30% over a life time.[12] Diabetes has been reported to modify the presenting features of pulmonary TB, but there are varying data, particularly regarding the association with lower lung field involvement. Feza Bacako Lu in her retrospective analysis stated that the presence of DM was found not to have an effect on patients' symptomatology. A higher number of insulin dependent DM patients presented with cavitary disease as compared with non diabetics controls. Lower lung field tuberculosis was significantly associated with female gender & in patients older than 40 years, was more frequently observed in diabetics[13]. In Diabetics, it has been suggested that TB tends to occur predominantly in lower lobes however no characteristic presentation is defined. TB patients with DM can present as acute and confluent type of infiltration with frequent cavitations & that hilar and basal areas of lung are involved more often.[14] On the other hand Goswami suggested that clinical presentation of

pulmonary TB is similar with or without DM and so is the bacteriological conversion rate and relapse.[15]

A study from Congo shows that diabetes appeared to have an induction and aggravating effect on TB. Tuberculosis was found to be more frequent in diabetes, had more pronounced radiological signs, treatment failure and frequent deaths.[16]

The problem of TB patients' management with diabetes is compounded by delay in diagnosis as both diseases share common symptoms such as lassitude, weight loss & anorexia etc. The possibility of concomitant diabetes should be considered in patients with poor clinical response to ATT. Like wise the suspicion of associated TB infection should be considered in patient with uncontrolled DM. Degree of control of DM does not influence the relapse rate but when relapses occur resistant strains are more often encountered in diabetes patients[14]. In one retrospective study Mona Bashar found that the diabetic patients were more than five times as likely to have infection with MDR-strain of TB.[17] It is observed that poorly controlled diabetes with high levels of glycosylated Hemoglobin, TB follows a more destructive course and is associated with higher mortality. [18]

Is immune dysfunction in Diabetics a Predisposing factor?

A probable cause of increased incidence of pulmonary TB in diabetics could be due to defect in host defenses and immune cell functions (Table-1), with predominately involvement of cell mediated immune response. In diabetics, infection with tubercle bacilli leads to further alteration in cytokines, monocyte – macrophages and CD4/CD8 T cell populations. The balance of T lymphocyte sub sets CD4 and CD8 plays a central role in the modulation of host defence against mycobacteria and has a profound influence on the rate of regression of active pulmonary TB.[19]

Do patients with TB have a higher prevalence of DM?

There is no definitive answer, however studies do show high prevalence of impaired glucose tolerance test in patients with TB with rates ranging from 2 to 41%[10]. It has also been shown that after effective ATT, 50% of them had normalization of glucose tolerance. In an old study published in 1957, Nichols surveyed 178 other wise healthy non diabetic military men with TB at Colorado , USA and showed that one third had abnormal glucose screening test and 5% had diabetes. He concluded that the incidence of diabetes among TB patients was considerably underestimated and that in TB patient, diabetes develops quite commonly[20]. The causes of increased susceptibility are not yet clearly understood. Some believe it to be due to reduced production of interleukin 1-beta and tumor necrosis factor alpha by peripheral blood monocytes in patients with TB or the non enzymatic glucosylation of tissue protein. In active pulmonary TB, reactive insulin C-peptide and glucose level before and after glucagon stimulation demonstrated absolute insulin deficiency and more frequent development of severe DM. The functional disorder of insular system of pancreas is more evident in middle aged & elderly patient with pulmonary TB. Plasma levels of interleukin-1 (IL-1) are also raised in severe illness and can stimulate anti insulin hormones. Serum levels of adrenocortico-tropin hormones (ACTH), cortisol, and T-3 have been found to be decreased in patients with tuberculosis. Clinical and sub clinical hypoadrenalism has been described frequently in these patients. These abnormalities make the patient's response to stress doubtful. The endocrine function of pancreas has been found to be adversely affected in severe tuberculosis and a higher incidence of chronic calcified pancreatitis occurs with concomitant DM and TB leading to an absolute or relative insulin deficiency state.

Effects of Anti Tuberculous Drugs on blood sugar level:

Rifampicin is a powerful inducer of the hepatic microsomal enzyme system & frequently interacts with other drugs. It lowers the serum level of sulphonylureas and biguanides.[21] Hence patients with co existing DM should have their doses of oral anti diabetic drugs

adjusted upwards according to plasma glucose concentration. Other Anti-TB drugs interfere rarely with blood sugar levels.

Principles of Management of Co-existent Tuberculosis & Diabetes.

Proper counseling is vital regarding disease course of patients with co-existing DM & TB. Patients with severe DM along with TB should be started on insulin therapy & once stabilized, shifted to oral hypoglycemic agents (OHA). Mild Diabetes needs only OHA. Vigorous & good chemotherapy is essential. Adverse effects of drugs need close monitoring. Isoniazid (INH) demands special attention with mandatory administration of pyridoxine (vitamin B6).

Patients with co-existant disease may need prolonged treatment, depending on diabetes control & treatment response.

Prophylaxis:

The Amercian thoracic society recommended in 1986, [22] that diabetics, particularly poorly controlled Insulin Dependent Diabetes Mellitus (IDDM) patients, should be given INH prophylaxis. Role of primary chemoprophylaxis and secondary prophylaxis in our community needs to be discussed.

Conclusion:

In Pakistan DM is on the rise and TB has one of the highest incidence in the world. There is emerging evidence that one disease is fuelling the other. The interest in diabetes and TB is mounting rapidly, so the clinician & researchers should prepare themselves to meet the challenges of the two disease combined.

References:

1. Barach JH. Historical facts in Diabetes: ANN Med Hist. 1928; 10: 387.
2. Lawrence Broxmeyer. Diabetes Mellitus, Tuberculosis & mycobacteria: Two Millenia of Enigma. Medical hypothesis 2005; 65(3): 433-39.

3. Winterbauer R, Bedon G, Ball W. Recurrent Pneumonia: Predisposing illness & clinical pattern of 158 patients. Ann Intern Med 1969; 70: 689.
4. Kirtland S, Winterbauer R, Dries D, et al. A clinical profile of chronic, bacterial pneumonia. Report of 115 cases. Chest 1994; 106: 15.
5. Lalit Kant. Diabetes Mellitus & Tuberculosis: The Brewing Double Trouble. Editorial: Indian J of TB 2003; 50 (4): 183-184.
6. Fatima Jawad. Debates in Pakistan . Diabetes voice July 2003; 48 (2): 12- 14.
7. Shera AS, Refique G, Khawaja IA, Ara J, Baqai S, King H: Pak National Diabetes survey: Prevalence of glucose intolerance and associated factors in Shikarpur, Sindh province. Diabet. Med 1995 Dec; 12 (12): 1116-21.
8. WHO Report: Global Tuberculosis Control, Surveillance, Planning & Financing: Country profile Pakistan : 2007: 125-8.
9. Ezung T, Devi NT, Singh NT, Singh TB. Pulmonary TB & Diabetes Mellitus: A study. J of Indian Med Association 2002 Jun; 100 (6): 378-9.
10. Ramachandran A, Snehalathac, Viswanathan V. Burden of Type 2 Diabetes & its complications. The Indian Scenario. Current science 2002; 83: 1471.
11. Patel JC. Complication in 8793 cases of Diabetes Mellitus: 14 years study in Bombay Hospitals, Bombay India . Indian Journal of Med. Sci. 1989; 43: 177.
12. Prof. P.V. Rao. TB & Diabetes - Nizam's Institute of Medical sciences Hyderabad , India : Indian Med- Sci. Hyd, India (Downloaded: Ourjeet.com Sandoz Business unit India)
13. Feza Bacakolu, Ozen Kacmaz, Gursel Cok, et al. Pulmonary TB in patients with Diabetes Mellitus. Respiration 2001; 68: 595-600.
14. M Mani Mala. Diabetes Mellitus & Pulmonary TB. Dibetes Forum 2006. (Downloaded: diabetesforum.net)

15. Goswami R, Kochcupillai N. Endocrine implication of TB. In: Sharma SK , Mohan A (Ed): Tuberculosis. New Delhi : Jaypee Brother Medical publication: 2001: 386.
16. Mboussa J, Monabeka H, kombo M, et al. Course of TB in Diabetics. Rev Pneumol clin 2003: 359 – 39.
17. Mona Bashar, Phil Alcabes, William N, N Ram. Increased incidence of MDR – TB in diabetic patients on the Bellevue chest service, 1987– 997. Chest Nov 2001; 120(5): 1514-19.
18. Amrit Guptan, Ashok Shah. Tuberculosis & diabetes: An appraisal. Ind J Tub 2000; 47: 3.
19. Yu CT , Wang CH, Huang TJ, et al. Relation of bronchoalveolar lavage, T-lymphocyte sub population to rate of regression of active Pulmonary TB. Thorax 1995; 50: 869.
20. Nichols GP: Diabetes among young TB patients. Am Rev Tubercle 1957; 10: 16 .
21. Acocella G, Canti R. Interaction of Rifampicin with other drugs. Tubercle 1980; 61: 171.
22. Rose D, Silver A, Sahechter C. Tuberculosis chemoprophylaxis for diabetes: are the benefits of Isoniazid worth the risk? Mount sinai Med J 1985; 52: 253.