Tuberculosis a deadly disease: A Review

Dr. Shashikant Agarwal[1]

1. Associate Professor, Department of Physiology, Jhalawar Medical College, India

Abstract:

The increase in cases of tuberculosis that has occurred with the increasing number of individuals infected with the human immunodeficiency virus (HIV) has focused attention on the problems in diagnosing and treating tuberculosis. While it is primarily considered a pulmonary disease, tuberculosis has the potential to infect almost every organ system via lymphohematogenous dissemination during the initial pulmonary infection. Immunocompromised individuals, such as patients with HIV, are at increased risk for extrapulmonary tuberculosis. The clinical manifestations are often nonspecific and insidious, and diagnosis may be delayed for years. Cases of miliary and meningeal tuberculosis are an exception, and they often constitute medical emergencies. Malnutrition is a one of the important cause of this disease. Malnutrition and tuberculosis are both problems of considerable magnitude in most of the underdeveloped regions of the world. It is important to consider, how these two problems tend to interact with each other. Measurement of activity of Adenosine deaminase enzyme (ADA) is a most reliable mean to detect tuberculosis accurately. Adenosine deaminase (ADA) is an endogenous tissue enzyme which is released into the serum in patients with many different types of malignancies and infections, including viral hepatitis, infectious mononucleosis, typhoid fever and tuberculosis. A high index of suspicion is needed to diagnose and treat extrapulmonary tuberculosis in a timely and health-preserving manner.

*Corresponding Author: Dr. Shashikant Agarwal, Department of Physiology, Jhalawara Medical College, India. E.mail: inbiosci@gmail.com.

Introduction:

TB is no longer the scourge it once was, but it remains an important cause of morbidity and mortality worldwide. Recent estimates are that 8-10 million new tuberculosis (TB) cases occur each year in the world. 2-3 million die. In developing countries, TB is one of the most common opportunistic infections in people who are seropositive for HIV-1[1] fueled by increasing poverty, homelessness, immigration, drug abuse, declining prevention programs, and the HIV epidemic, its incidence in the developing and developed countries has increased dramatically. The deadly synergy between *Mycobacterium tuberculosis* and the human immunodeficiency virus (HIV) has resulted in a resurgence of tuberculosis world over. The impact of this "cursed duet" in human suffering has been enormous. With HIV making rapid inroads in India, the specter of dual infection with HIV and tuberculosis in going to be a daunting prospect.

Strict distinction between "adult" and "childhood" patterns of TB should be avoided

[2]. Pleural effusion develops because of excessive filtration or defective absorption of accumulated fluid. Effusion may be a primary manifestation or a secondary complication of many disorders. Tuberculosis (TB) is a major cause of pleural effusion, which in TB usually has lymphocytic and exudative characteristics [3].

Extra pulmonary tuberculosis usually presents more of a diagnostic problem than pulmonary tuberculosis. In part this relates to its being less common and, therefore, less familiar to most clinicians. In addition, extra pulmonary tuberculosis involves relatively inaccessible sites and because of the nature of the sites involved, fewer bacilli can cause much greater damage. The combination of small numbers of bacilli and inaccessible site cause bacteriologic confirmation of a diagnosis to be more difficult, and invasive procedures are frequently required to establish a diagnosis.

Tuberculous meningitis remains an important cause of morbidity and mortality in India. Due to lack of early and timely diagnosis of *Tuberculous meningitis*, the fatality remains high, even when it is not fatal, the sequel are distressing and disabling. Thus, early and correct treatment is essential for a successful outcome in patients of *Tuberculous meningitis*.

Among the extra pulmonary presentations, pleural TB is second in frequency after tuberculous lymphadenitis. Exudates are due to pleural inflammation (pleurisy), with an increased permeability of the pleural surface to proteinaceous fluid. Inflammation or injury increases pleural membrane permeability to proteins and various types of cells and leads to the formation of exudative effusion. In general, exudates generally have protein concentration higher than 3 g/dL or a specific gravity of 1.020 on a refractometer [5, 6]. Lymphatic obstruction may also contribute to accumulation of pleural fluid [7].

Population	1049 Million
Global rank(by estimated number of cases)	1
Incidence(all cases/100000 population)	75
Prevalence (Smear +ve/ 100000 population)	156
TB Mortality per 100000 population	37
Percentage of adult (15-49 yrs)TB cases HIV positive	4.6
Percentage of New cases multi drug resistant	3.4

Table 1: The tuberculosis estimates of India (2002)

Nutrition and Tuberculosis

Infectious disease and malnutrition are major health problems in the developing world. Malnutrition can predispose to the development of a variety of infections. Malnutrition and tuberculosis are both problems of considerable magnitude in most of the underdeveloped regions of the world. It is important to consider, how these two problems tend to interact with each other. The term consumption has been virtually synonymous with tuberculosis

throughout the history1 and the link between tuberculosis and malnutrition has long been recognized; malnutrition may predispose people to the development of clinical disease and tuberculosis can contribute to malnutrition [2]. Before the advent of antituberculosis chemotherapy, a diet rich in calories, proteins, fats, minerals, and vitamins was generally considered to be an important, if not essential factor in treatment of tuberculosis. The introduction of specific antituberculosis drugs, however, has so radically altered the

management of the disease that the role of diet should be considered in the light of the advances in treatment. Furthermore, protein energy malnutrition (PEM) is an important predisposing factor for the development of tuberculosis. Thus, several aspects related to nutrition have a profound impact on the pathogenesis and outcome in patients with tuberculosis.

It is well established that PEM adversely affects the host's immune response to mycobacterial infection. Evidence is also available suggesting that malnutrition adversely affects the lung structure and function. Die *et al* [8], studied low protein guinea pigs vaccinated with *Mycobacterium tuberculosis* H37Ra and reported that dietary protein malnutrition impairs vaccine – induced resistance to mycobacterium tuberculosis in part by altering the cytokine profile to favor macrophage deactivation. Chan *et al* [9] observed that mice fed a two percent protein diet that developed protein calorie malnutrition rapidly succumbed to infection with mycobacterium tuberculosis compared to well nourish controls receiving a 20 percent protein diet. Malnourished mice exhibited a selective, early, tissue specific diminution in the expression of interferon –γ (IFN-γ), tumour necrosis factor α (TNF-α) and the inducible form of nitric oxide synthatase in the lungs. A marked diminution of the granulomatous reaction was also observed in the lungs, liver and spleen throughout the entire course of infection. Importantly, they observed that the progressively fatal course of infection observed in the malnourished mice could be reversed by restoring a full (20%) protein diet. These results indicate that PEM selectively compromises several components of the cellular immune response that are important for containing and restricting tuberculosis infection and these changes can be reversed or ameliorated by nutritional intervention. Thus, PEM is an important predisposing factor for the development of tuberculosis especially in children.

WHO Region	Incidence[a]				Prevalence[a]		TB Mortality	
	All forms		Smear positive[b]					
	No. (Thousands) (% of global total)	Per 100000 pop	No. (Thousands)	Per 100000 pop	No. (Thousands)	Per 100000 pop	No. (Thousands)	Per 100000 pop
Africa	2573 (29)	356	1098	152	3741	518	587	81
America	363 (4)	41	161	18	466	53	52	5.9
Eastern Mediterranean	645 (7)	122	289	55	1090	206	142	27
Europe	445 (5)	50	199	23	575	65	69	7.8
South East Asia	2967 (33)	182	1327	81	4965	304	535	33
Western Pacific	1925 (22)	111	865	50	3765	216	307	18
Global	8918 (100)	140	3939	62	14602	229	1693	27

[a]Incidence- New cases arising in given period; prevalence – the number of cases which exist in the population at a given point in time.
[b]Smear positive cases are those confirmed by smear microscopy, and are the most infectious cases.

Table 2: Estimated incidence, prevalence and TB mortality, 2004

Malnutrition is well known to produce effects on pulmonary function and immunological parameters. Malnourished patient are more prone to develop antituberculous treatment induced hepatotoxicity. Tuberculin energy is commonly observed in severely malnourished patients.

Tuberculosis adversely affects the nutritional status in several ways. These effects are more profound in the setting of co-infection with HIV. Both HIV status and malnutrition significantly contribute to atypical presentation of pulmonary tuberculosis. This results in a delay in the diagnosis and starting of specific antituberculosis treatment. Energy requirements are substantially increased in patients with tuberculosis as in the case of other infections. Complications of tuberculosis and side effects of antituberculosis treatment such as hepatotoxicity further interfere with adequacy of nutritional intake and retention of nutrients. Poor nutritional status has been observed in patients with various forms of tuberculosis in several published studies. In the study reported by Kennedy *et al* [10] of the 200 adult Tanzanin patients with sputum smear positive pulmonary tuberculosis studied, 77 percent males and 58 percent females had a body mass index (BMI kg/m^2) below 18.5 and about one fifth had a BMI below 16.

Adverse effects of tuberculosis on nutritional status

- *Increased energy expenditure*
  o Increased work of breathing
  o Chronic infection
  o Medical treatment (e.g. bronchodilators, chest physical therapy)
- *Reduced intake*
  o Fluid restriction
  o Shortness of breath
  o Anorexia due to chronic disease
  o Gastrointestinal distress and vomiting
- *Additional limitations*
  o Lack of financial resources
  o Impaired feeding skills (for infants and children)
  o Altered metabolism

Handa [11] used Onodera's prognostic nutritional index (PNI; 10X serum albumin concentration + 0.005 x peripheral lymphocyte count) as a parameter to check the nutritional status and immunological deficiency in 451 patients with pulmonary tuberculosis. He (Handa) observed that the PNI was also low in patients with negative tuberculin reaction and increased with intensification of positive reaction. The PNI values also significantly increased following sputum conversion.

Sharma *et al* [12] reported that patients with multidrug resistant tuberculosis (MDR-TB) (n = 19) had a mean BMI of 17.1. Ten of 19 patients had BMI less than 17.5. These patients also had a significantly lower mid arm circumference, triceps skin fold thickness compared to normal control subjects. Yoneda [13] reported that PEM was more prevalent and more severe in patients with chronic intractable pulmonary tuberculosis compared with newly diagnosed patients with drug sensitive tuberculosis. The grade of malnutrition was significantly associated with the reduction in delayed-type hypersensitivity response, ratio of CD4+ / CD8+ T-lymphocytes, interleukin – 2 (IL - 2) production by peripheral blood mononuclear cells and natural killer (NK) cell activity, CD 30 is a putative marker of Th2 cytokine producing cells

Hanekom *et al* [14] postulated that tuberculosis disease severity and nutritional status would alter the cytokine responses and therefore, the SCD 30 levels. They reported significantly higher SCD 30 levels in the presence of nutritional compromise in children with tuberculosis suggesting the presence of Th2 cytokine response.

Mehta *et al* [15] reported that nutritional status as reflected by the patient's serum albumin and haemoglobin was the best predictors of survival. They suggested that early and aggressive attention to improve the patient's nutritional status is an important intervention in salvaging these patients.

Macallan *et al* [16] investigated the whole body energy and protein metabolism in nine subjects with pulmonary tuberculosis and six undernourished subjects (BMI < 18.5) and seven control subjects from Indian population. They reported that tuberculosis did not increase fasting whole body protein turnover but impaired the anabolic response on feeding compared with control and undernourished subjects. They suggested that such "anabolic block" may contribute to wasting in tuberculosis and may represent the mechanism by which some inflammatory states remain refractory to nutritional support.

Vegetarian diet has been implicated as a risk factor for tuberculosis. There was a trend towards increased risk of tuberculosis with decreasing frequency of meat or fish consumption. The trace elements comprise metals in biological fluids at concentrations less than 1 µg/g wet weight. Most are essential nutrients for humans. Zinc is a prominent modulator of the immune system and is known to compromise neutrophil functions and cases impaired all mediated immunity (CMI). It is thought to play an important role in host response to mycobacterium tuberculosis by virtue of its effect on the CMI. Several studies reported low serum zinc levels in patients with pulmonary, disseminated, lymphnode and neurological tuberculosis. The cause of low serum zinc levels in patients with tuberculosis is thought to be multifactorial. Liberation of endogenous mediators from polymorphonuclear leucocytes in the setting of chronic infection results in a net flow of amino acid and zinc to the liver for the synthesis of metalloenzymes. This change in distribution of zinc in the body leads to hypozincaemia. It has also been postulated that zinc may be utilized by the mycobacterium tuberculosis for growth and multiplication. Accumulation of zinc at the site of tuberculosis lesions has also been demonstrated. Malnutrition associated with tuberculosis could also contribute to hypozincaemia. Altered excretory pattern of zinc and decreased absorption of zinc from the gastrointestinal tract are the other postulated mechanism. In some studies significant improvement in plasma zinc levels has been reported with antituberculosis treatment while in others this finding has not been observed. Elevated whole blood copper and the plasma copper levels have been reported in patients with tuberculosis. Altered intestinal absorption, altered excretion, changes in distribution, altered carrier protein concentrations and interactions with invading microorganisms have been postulated as mechanism responsible for this observation.

Mycobacterium requires iron for their survival within a host. They synthesize and utilize specific affinity iron binding compounds which help them grow in the iron restricted conditions of the host.

Mycobacterium produces two types of iron binding substances called exochelins and mycobactin. Exochelin act as scavengers and Mycobacten occurs in the cell wall and it's concerned with the transport and storing of iron. Iron deficiency and iron overload have both been found to predispose to the development of infections. Iron deficiency impairs the immune response and increases susceptibility of the host to infections. Some workers have explored the role of silicon in the pathogenesis of tuberculosis. In silicon deficiency mice, delayed type hyper sensitivity (DTH) response to tuberculin was also reduced. Addition of silicon to the diet of silicon deficient mice corrected antituberculosis immunity.

Available evidence suggests that vitamin A has an immunoprotective role against human tuberculosis. Deficiency of vitamin A and C has been considered to be predisparing factor for the development of tuberculosis. Patients with tuberculosis have been found to have low level of vitamin A in several studies. Honecom *et al* [14] reported that South African children with tuberculosis had low plasma vitamin A levels (Mean 18.1 µg/dL ; SD 10.3 : 62% below normal). More extensive disease and those with severe disease had lower levels of retinal binding protein, prealbumin and albumin.

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Preliminary available evidence suggests that the additional administration of antioxidants such as tocopherol acetate, galascorbin and antihypoxic agents such as piracetam, piriditol may have a beneficial role in the treatment of destructive pulmonary tuberculosis.

Haemotological manifestation of tuberculosis

Morris *et al* [17] observed anemia in 60% of the patients, males being more frequently affected than females. In 95% of cases the anemia was normocytic and normochronic. The red cell distribution width has been found to be moderately increased which normalized with treatment of infection.

The cause of low haemoglobin level in pulmonary tuberculosis is considered to be multifectorial. Bone marrow iron has been found to be decreased in studies of Baynes *et al* [18], Camerson and Home [19], Similarly, Serum iron and total iron binding capacity have been observed to be decreased in patients with pulmonary tuberculosis and anemia compared to those without anemia. Further, bone marrow non-haeme iron was found to be greater, suggesting decrease release of marrow iron stores and suppression of erythropoesis by inflammatory response mediators. Ebrahim *et al.* [20] recently found that the erythropoetin level low in patient with both pulmonary tuberculosis and anemia and suggested that the blunted erythropoetin response in these patients was due to the inhibitory effect of tumour necrosis factor-α (TNF-α). This cytokine is released during the course of inflammatory process. Macrocytic anemia is less frequently associated with pulmonary tuberculosis. Serum vitamin B_{12} levels were pulmonary were found to be higher in upto 57% of the patients with pulmonary tuberculosis. Knox-Maculay [21] found no association between serum vitamin-12 levels.

Morris *et al* [17] found mild leucopenia with count less than 4×10^9/L has been documented in 1.5 to 4% of pastients and mild leucocytosis occurred in eight to forty percent of patients.

Patients with advanced tuberculosis had higher counts, than those with minimal disease.

Relative neutrophila has been observed in one third to one half of patients [22]. Decreased in the peripheral blood CD 4+ subset of T-lymphocytes has also been documented and the decreased count return to normal level following successful treatment [23].

The reversal of lymphopenia following chemotherapy favours the concept that the lymphopenia is tuberculosis is caused by recruitment of CD_4+T-lymphocytes to the sites of granuloma formation [23] mild, absolute or relative monocytosis has been also been observed in some series. Isolated thrombocytopenia is rare in pulmonary tuberculosis and its pathogensis is believed to be immune mediated [24].

Coagulation abnormalities in patients with tuberculosis are not well documented. Variable abnormalities in the coagulation system have been described in some studies. Disseminated intravascular coagulation (DIC) has been documented in miliary tuberculosis and has a variable fatality rate.

Tuberculosis produces a spectrum of histopathogical reaction in the bone marrow. They range from normal marrow hyperplasia and necrosis of the marrow. The bone marrow in patients with untreated tuberculosis may show megaloblastic changes and this could be a reflection of poor nutritional status of these patients. Iron stores estimated on bone marrow aspirates bear a good correlation with serum iron level. Patients with poor nutritional status may have decreased iron status on bone marrow examination.

Biochemical Markers for Diagnosis:

Adenosine Deaminase in CSF, Pleural fluid and Ascitic fluid

ADA isoenzymes are widely distributed in human tissues in three forms, soluble and interconvertible (small, intermediate and large in

relation to its molecular weight). The activity of ADA is times greater in lymphocytic cell and than in erythrocytes and, in relation to the former is greater in T-lymphocytes than in B-lymphocytes and varies during T-cell differentiation with significant increases of its level in immature or undifferentiated states.

The ADA, isoenzymes are found highest activity in lymphocytes and monocytes, whereas ADA, isoenzyme gene products appears to be found only in monocytes. The assay of ADA activity in pleural and other effusion is very useful in differential diagnosis especially is the case of tuberculosis which is characterized by an increase in activity.

Adenosine deaminase (ADA; adenosine amino hydrocase, EC 3.5, 4.4) catalyzes the deamination of adenosine and deoxyadenosine to inosive and deoxyinosive [25]. Human ADA exists in at least three molecular forms. ADA is a monomeric protein with a molecular mass of n35 kDa (gene assignment, chromose 20). $ADA_2 + CP$ (molecular mass ~ 280 k Da) is composed of two ADA_1 molecules connected via a combining protein (CP; binding protein) (gene assignment, chromosome 2 and 6). Third isoenzyme, ADA_2 appears to be coded by a separate gene locus of unknown chromosomal position [26].

Serum ADA activity is increased in various diseases such as liver disease, tuberculosis typhoid, infective mononucleosis and certain malignancies especially those of hemopoetic origin. The origin of serum ADA and the mechanism by which serum activities are increases have not been fully elucidated. Usually total ADA activity is measured without determining the contribution of each isoeyzymes. Because of unique distribution and characteristics of the ADA isoenzymes, it is essential for interpretation of results to determine the contribution of each of the total activity. The methods used to distinguish between two isoenzyme are generally based on the ratio of activity, using the two substrates adenosive and deoxyadenosive respectively. These tests are,

however only an approximation of the real isoenzyme pattern and cannot distinguish between ADA_{1m} and ADA_{1c}.

Piras *et al*. [27] consider ADA as a Marker of cell mediated immunity, with an increase in its serum level in different diseases. Regarding its main physiologic activity, ADA is related to lymphocytic differentiation and proliferation, showing a significant increase in its values during the mythogenic and antigenic response of lymphocyte [28].

Cellular immunity mediated by T-lymphocytes constitutes a major defense against tuberculosis. Adenosine deaminase estimation in pleural fluid is occasionally Useful [3]. Adenosine deaminase, called ADA by Spencer et al [29] is an enzyme catalyzing conversion of adenosine to inosine in the purine pathway. It has an extremely important physiological ole in the lymphoid tissue evidenced by its extremely high concentration in lymphocytes, particularly T-cells. Adenosine deaminase has shown promising results in the diagnosis of tuberculous pleural, peritoneal and pericardial effusions and tuberculous meningitis. Adenosine deaminase (ADA) is an endogenous tissue enzyme which is released into the serum in patients with many different types of malignancies and infections, including viral hepatitis, infectious mononucleosis, typhoid fever, and tuberculosis. In pleural fluid, elevated ADA levels are very commonly associated with tuberculosis. In CSF, ADA is elevated in cases of tuberculous meningitis [30,31]. It is reported that it is a pleural fluid marker for tuberculosis. The analysis of PCR and ADA activity, however, is a very useful diagnostic approach to achieve a more rapid and precise diagnosis in the cases of pTB [32]. It is found that Pleural fluid ADA levels in TB effusions were significantly higher than the non-TB effusions [33]. The molecular forms of ADA were studied [34] that in pleural effusions using the technique of SDS-PAGE. Analysis of the Adenosine deaminase in pleural fluid pinpoints many pulmonary and systemic diseases are known to cause pleural effusions.

Drug-resistant strain of tuberculosis

An extensive international study published by the Lancet medical journal shows that the illness, once thought to be the stuff of books by the likes of Charles Dickens, is making a quiet comeback. Cases of tuberculosis in Africa, Asia, Europe and Latin America are on the rise, and many of them are of a strain resistant to vaccination [35].

The study examines two types of tuberculosis: Multi drug-resistant (MDR) and extensively drug-resistant (XDR), both of which are far more widespread than previously believed, experts claim. MDR tuberculosis is resistant to at least two first-line drugs – Isoniazid and Rifampicin – used as primary treatment in confirmed cases of the disease. XDR is resistant not only to these two, but also to an antibiotic used as second-line drug.

According to the study, TB strains resistant to any second-line drugs were found in nearly 44 percent of patients: From 33 percent of cases in Thailand to 62 percent of cases in Latvia. XDR tuberculosis was found in 6.7 per cent of all patients in the study. Rates in South Korea and Russia, at 15.2 and 11.3 percent respectively, were more than twice the global estimate made by the World Health Organization.

The highest prevalence of MDR tuberculosis documented to date – 47.8 percent – was reported in 2011 in Minsk, Belarus, according to the Lancet study. Though infection rates vary greatly between countries, scientists warn against stereotyping the disease as an issues solely of poorer, less developed nations: "MDR tuberculosis is not an issue isolated in one city or country, but reflects a wider public health threat resulting from severely resistant forms of M tuberculosis. To adequately address MDR tuberculosis, more solid epidemiological information is needed to increase overall understanding of disease development and transmission," (Sven Hoffner wrote in Lancet).

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