



# SAARC

(South Asian Association for Regional Cooperation)

Journal of Tuberculosis, Lung Diseases and HIV/AIDS



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## Editorial

Global HIV epidemic has emerged as a formidable challenge to public health, development and human rights. Since the beginning of the epidemic, approximately 30 million people have lost their lives due to HIV related causes. These deaths mean an incalculable loss of human potential and are associated with enduring trauma for the community, particularly for the loved ones in the individual households. Hence, HIV/AIDS causes significant emotional and psychological costs at individual and household levels.

Year 2010 is the targeted timeline for providing universal access to HIV prevention-treatment-care & support continuum by adhering to rights based approach. Obtaining essential health care services by the needy people is regarded as a fundamental human right. The provision of treatment care and support to people living with HIV/AIDS is also considered as one of the most important approach in HIV/AIDS prevention. Hence, the entire world has been focusing on various aspects of HIV prevention in order to halt and reverse the HIV epidemic by 2015 as per the Millennium Development Goal-06.

According to the latest data of UNAIDS, the estimated number of persons living with HIV/AIDS in the world in 2009 was 33.3 million. South Asia had an estimated number of 2.45 million HIV positive people in 2009. An estimated 2.6 million uninfected persons in the world became infected during the year 2009 and 1.8 million died due to HIV/AIDS related causes in the same year. For the first time in the 30 year history of HIV/AIDS Pandemic, UNAIDS declared that the world has halted the epidemic and begun to reverse it. However, we have to understand that the epidemic in South Asia can not be reversed without an effective, efficient and realistic programme on reducing the rate of new infections.

Prevention of HIV remains the mainstay of the global, regional and national responses. However, only 50% of countries in the world with targets for universal access have targeted for HIV prevention strategies in 2010. This means, many people at risk of HIV infection lack meaningful access to tailored prevention services. Countries with different epidemic patterns will require tailor-made national response to achieve successful HIV prevention. Some countries adopt to use data on modes of transmission as the basis for formulation of evidence-based prevention programmes. This model proves to be helpful in developing action plans to stop occurrence of new infections and also to prioritize the allocation of limited resources.

The HIV prevention programmes are said to be effective when they have been planned and implemented by considering the following aspects of the epidemic:

### **1. Better knowledge on most at risk populations in the locality:**

HIV epidemic in Asia is fuelled by unprotected paid sex, sharing contaminated injecting instruments by injecting drug users and unprotected sex among men who have sex with men.

The largest infected population consists of men who buy sex and most of them are married or awaiting marriage. This means, a significant number of women who often are perceived as low-risk, are at significant risk of infection. Therefore, countries need to look deeply at individual epidemic pattern to plan their prevention activities.

### **2. Addressing contextual factors:**

To make a difference, the prevention programmes should address not only risk factors but also the factors recognized as important in prevention of HIV new infections such as cultural expectations of men and women, violence against women and girls, power differences in intimate relationships etc.



Therefore, the prevention strategies should adequately address the social norms that make risky behaviours acceptable, in order to reduce the occurrence of new infections effectively.

### **3. Focus on identified high burden areas:**

Each country needs to focus on the geographical distribution of the areas where most new infections are likely to occur in order to achieve the success in curtailing new HIV infections.

### **4. Increasing and sustaining resource allocation for HIV prevention:**

The entire world is focusing on “virtual elimination of mother-to-child transmission of HIV” to prevent babies from being born with HIV. The countries have to increase and sustain funding for prevention aspects of the HIV programmes which may not only eliminate mother-to-child transmission of HIV but also eliminate the newborns become orphans because of HIV.

In many parts of the world, funding aimed at most at risk populations is inadequate and not on par to their contribution to new infections. Sometimes, funding does not support the most important contextual factors. The sources of new infections are different in different countries in the world. In Nepal, approximately 41% of reported HIV positives are seasonal labour migrants returning from India and another 21.5% of reported positives are spouses of those migrants in rural areas. In Uganda, a study on mode of transmission found that significant HIV transmission has occurred among married cohabiting couples. That study finding has paved the way for a special campaign to promote HIV Counseling and testing among couples in Uganda.

HIV prevention needs a strong leadership. A leadership that is robust enough to address the harmful social norms and practices. The leadership should be able to mobilize communities to take collective responsibility of HIV prevention and its sustainability overtime because HIV/AIDS means struggling with the triple burden of disease, stigma and poverty. So, let us mark the beginning of a massive campaign on this World AIDS Day 2010 among South Asians to urge them to safeguard their health in turn to see a HIV/AIDS free SAARC Region by halting and reversing HIV/AIDS epidemic by 2015.

# TUBERCULOSIS: STUDIES ON ROLE OF GENDER, AGE AND DRUG ADDICTION IN EASTERN PART OF INDIA

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## ABSTRACT

**Objectives:** The objective of the present investigation was to determine the socioeconomic conditions, age and gender relations to tuberculosis with evaluation of drug (smoking/ alcohol) influences on it and correlate the clinical data to an animal experiment result of antioxidant system of drug treated male rats.

**Settings:** The investigation was carried out in a rural and an urban part of Eastern India.

**Methodology:** Acid-fast bacillus (AFB) staining of sputum was performed in rural Indpur (total human individuals 498, male 384) and urban area Kamarhati (total 1017, male 735) following WHO guidelines. Catalase, superoxide dismutase (SOD) activities and level of non-protein soluble thiol (NPSH), malondialdehyde (MDA) were measured in lung of rats exposed four weeks to nicotine (0.2 mg/kg s.c.) and/or ethanol (20% [w/v] at 3 g/kg orally).

**Results:** Mean AFB score was greater in all age groups of Kamarhati. Smoking/ alcohol alone significantly and synergistically even in greater extent increased TB severity in both places, furthering it in backward classes. Drug treatment significantly increased MDA level and SOD activity with a decrease in NPSH level and catalase activity in rat.

**Conclusions:** Males are greater sensitive to TB and urban area is affected more. Clinical findings paralleled with animal experiments pointing the disastrous consequences of nicotine. Up-gradation of socioeconomics in rural area, avoiding of reckless unscientific changes of demographic profile of a region, and minimization of pollutions in urban areas may diminish disease outbreak.

**Key words:** Tuberculosis, Rural and urban, Risk factors, Antioxidant systems, Rat lung

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## INTRODUCTION

People of lower income group (LIG) in developing countries are prone to different chronic infections like gastroenteritis, respiratory tract infections, malaria, tuberculosis, and HIV/AIDS in recent years.<sup>1,2</sup> Tuberculosis (TB) causes approximately two million deaths globally per year, more than 90% of which

occur in developing countries.<sup>3</sup> In spite of multi drug therapy, BCG (Bacillus Calmette-Guérin) vaccination and other chemotherapeutic advancements, TB is still the second leading cause of death.<sup>4</sup>

Several investigations identified the risk factors for TB, but fewer in India.<sup>5</sup> Scanty reports reveal that the TB sensitivity could be associated with environmental, economic and life-style factors which have been minimized in American and European communities.<sup>6,7</sup> In developing countries like India, the decline in risk factors is confined to the middle and high socioeconomic groups. Recently, several government and NGO operated program have been adopted fruitfully.<sup>8</sup> Different techniques like ELISA or genomics tools are utilized for confirmed diagnosis of TB, but rapid diagnosis by sputum staining of acid-fast bacilli (AFB) is still useful for a large number of patients.<sup>9</sup> Recently, few rural and metropolitan areas were selected in the Eastern part of India for the present investigation.

## OBJECTIVES

i) To make comparison between the TB sensitivity in rural and urban areas ii) to assess the disease sensitivity (by AFB staining procedure) in relation to gender, age, drug addiction and economic status of individuals iii) as it is evident that chronic ethanol and/or nicotine administration could result impairment of rat antioxidant system<sup>10</sup>, here male rats were treated with nicotine and/or ethanol and tested their lung antioxidant profile. These results were extrapolated to explain the clinical data on addiction associated disease sensitivity.

## MATERIALS

Bovine serum albumin (BSA), thiobarbituric acid (TBA), nicotine, reduced glutathione (GSH), 5-5'-dithiobis-2-nitro benzoic acid were purchased from Sigma chemicals (St. Louis, MO, USA). Sodium dihydrogen phosphate ( $\text{NaH}_2\text{PO}_4$ ), disodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4$ ), ethylenediamine tetraacetic acid (EDTA), pyrogallol, basic fuchsin, ethylene Blue, ethyl alcohol, and other chemicals used in the present investigation were of analytical grade and purchased either from SRL, India or E. Merck, India.

## METHODS

### Study design

This is a comparative assessment of TB sensitivity between an urban and rural area with relation to patients' age, sex, drug addiction and economic status. Clinical data has been correlated to a rat experiment on the status of drug induced lung antioxidant system

### Settings

The data were collected from Indpur, a rural and intermediate Panchayat of Bankura district and from Kamarhati which is an urbanized city of North 24 Parganas district, operated by the municipality and a certain part of the area covered by Kolkata Metropolitan Development Authority (KMDA).<sup>11</sup>

### Study period

The data was collected and laboratory experiment was carried out in the period of 2005 to 2009.

### Study population and selection of subject

The patients and participants of this investigation were routinely diagnosed in the specialized TB division / centers in the respective block hospital of Indpur and Kamarhati. They were selected at random irrespective of their ethnicity, caste, gender and ages. But those individuals were excluded who were affected with severe diabetes, cardiovascular and chronic kidney disease or some other chronic infectious diseases.

### Sample size, method of sampling and data collection

In rural Indpur, a total 498 diagnosed (male 384) and in urban area Kamarhati a total 1017 diagnosed (male 735) voluntarily participated in the present investigation. An apparently large number of individuals from several years were utilized here to minimize the intra-individual variability and possible deviations caused by some intrinsic factors. The socio-economic profiles of the participants were collected by standard questionnaire method. Here, all participants were distributed in four age groups;  $\leq 15$ , 16-30, 31-45 and  $\geq 46$  years. Data of all three elder groups were compared with the corresponding  $\leq 15$  year's age group of each sex. To verify the influence of economic condition, individuals of both sexes of all

ages were arranged in 1+, 2+, 3+ and 4+ AFB scoring groups and their yearly incomes are compared in relation to their disease severity. All data and samples were handled by registered health professionals after prior permission of the concerned Institutional Ethical Committee. The sensitivity to TB was estimated by acid-fast bacillus staining.

### **Acid-fast Bacillus (AFB) staining of sputum sample**

Three sputum samples (twice in successive mornings and once as spot collection on the second day) were collected from each subject. Those were stained by traditional Ziehl Neelsen (Z-N) method using carbol fuchsin, acid-alcohol and ethylene blue solutions.<sup>9,12</sup> The Indian Government laid guidelines on Revised National Tuberculosis Control Program (RNTCP) and World Health Organization (WHO) protocol were followed in evaluating the AFB scores.

### **Animals and drug treatment schedule**

Male rats of Wister strain, weighing 120-140 g were housed in the OIST animal resource facility and provided with rodent chow and water for one-week prior use. A total 24 rats were randomly separated in 4 groups having 6 in each. Drugs were treated for 4 weeks as follows: (1) Control rats were administered normal saline orally; (2) nicotine was administered subcutaneous (s.c.) at a dose of 0.2 mg/kg; (3) ethanol (20% [w/v]) was given orally at a dose of 3 g/kg; and (4) ethanol and nicotine were administered by the route and with the dose described above. Present treatment schedule was standardized after several dose responses testing in our laboratory.<sup>10</sup>

### **Tissue cytosol preparation and oxidative stress studies in rat lung**

The animals were sacrificed on time and their lungs were dissected, washed with ice-cold NaCl (0.9%, w/v) and frozen at -20°C until use. Those were homogenized in 0.1 M chilled phosphate buffer (pH 7.4). Fractions of fresh homogenates were utilized for few experiments. The rest of the homogenates were spun at 10,000 x g for one hour in a cold centrifuge. Cytosol was preserved at -20°C in several aliquots.

### **Determination of catalase activity**

The catalase activity from lung cytosol was measured

spectrophotometrically. The rate of degradation of H<sub>2</sub>O<sub>2</sub>, the substrate of this enzyme was observed at 240 nm.<sup>13, 14</sup>

### **Determination of superoxide dismutase (SOD) activity**

The SOD activity from lung cytosol was determined according to the method of Marklund and Marklund (1974). The activity was expressed in unit 'U', assuming, that activity of enzyme as one unit (U) which inhibits auto-oxidation of pyrogallol by 50%.<sup>14, 15</sup>

### **Estimation of non protein soluble thiol (NPSH)**

The NPSH in lung homogenate was determined by standard DTNB (5, 5'- dithiobis-2-nitrobenzoic acid) method as initially described by Ellman (1959) with a slight modification.<sup>16-19</sup> In brief, lung tissues were homogenized with 50 mM Tris buffer, pH 7.5, containing 250 mM sucrose and 5 mM EDTA. The protein of 10,000 x g supernatant was precipitated by sulfosalisalic acid and clear cytosol was added to 0.1 M sodium phosphate buffer containing 5 μM DTNB. The level of NPSH was determined against a GSH standard curve.

### **Estimation of malondialdehyde (MDA)**

Tissue homogenates were utilized for MDA assay by the method of Buege and Aust (1978) with a slight modification. To chelate iron and reduce its interference in peroxidation reaction of unsaturated fatty acid, 1 mM EDTA was used in the reaction mixture. To reduce the interference caused by a yellow-orange color produced by some carbohydrates, the reaction mixture was heated at 80°C instead of 100°C. Finally the MDA was measured and calculated utilizing the molar extinction coefficient of MDA (1.56 x 10<sup>5</sup> cm<sup>2</sup> / mmol).<sup>20, 21</sup>

### **Protein assay**

Proteins were estimated in all tissue samples by the method of Lowry (1951) using bovine serum albumin (BSA) as the standard protein.<sup>22</sup>

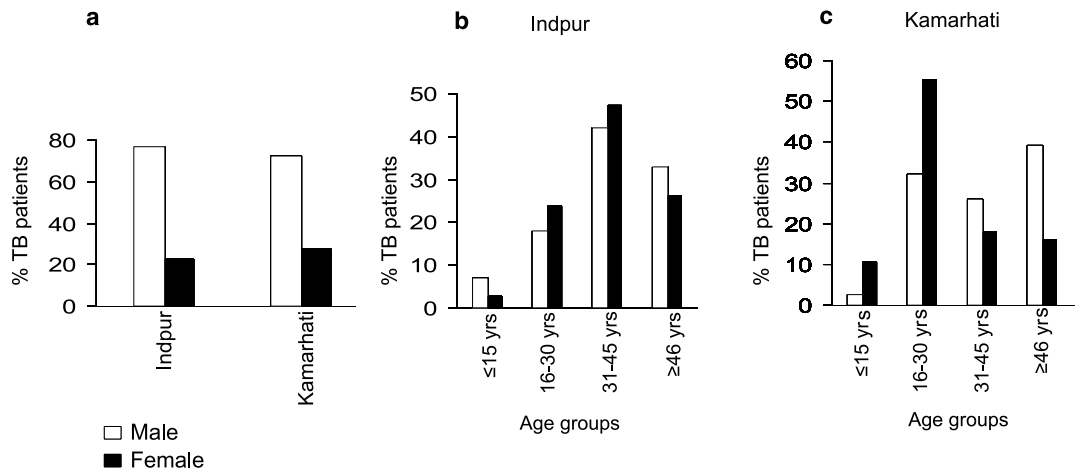
### **Statistical analysis**

The data were statistically analyzed using Student's t-test (Fisher and Yates 1974).<sup>23</sup>

## RESULTS

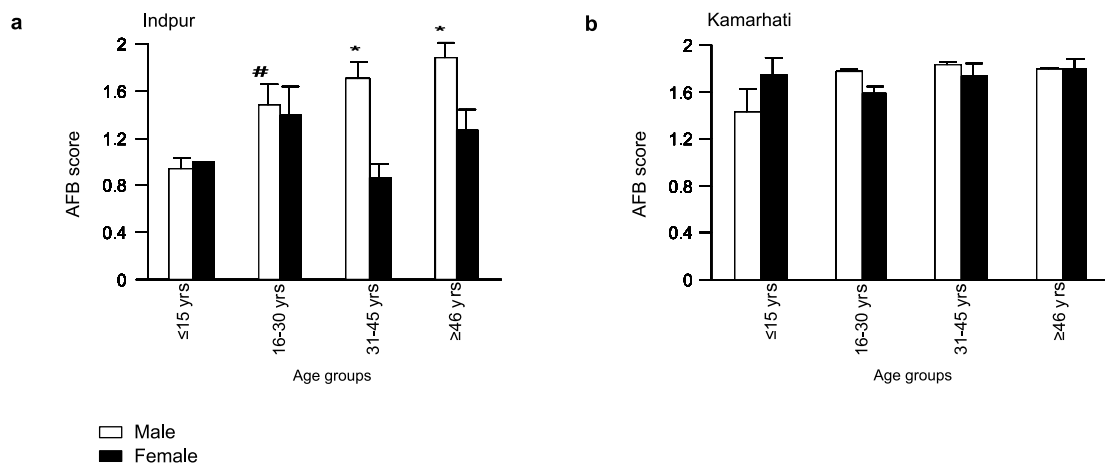
In Figure 1 the occurrences of TB in male and female (78% and 22% respectively) are very similar in Indpur and Kamarhati whereas, it differs in different age groups of two locations. Only in Indpur, a proportionate

increase of both male and female patients' number was observed in 16-30 and 31-45 years groups. In Kamarhati, the male patients of 16-30, 31-45 and  $\geq 46$  year's groups showed similar occurrences (29-39%). And in female, 57.1% diagnosed belong to 16-30 years group.



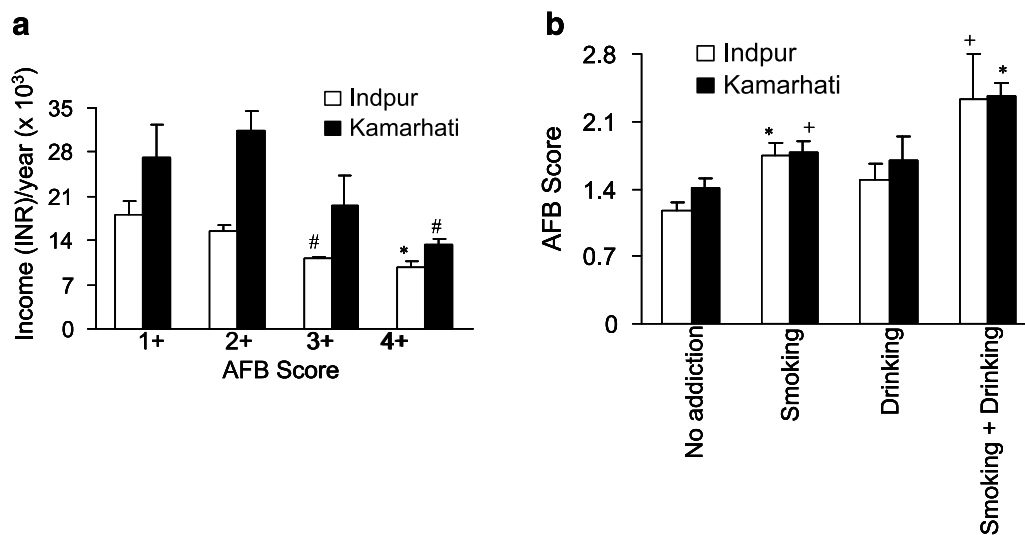
**Figure 1.** The percentage of male and female TB patients attendees of rural Indpur (sample size  $n = 498$ ; male 384) and urban Kamarhati (sample size  $n = 1017$ ; male 735) areas (a). Percentage of same patients in different age groups of Indpur (sample size of different age groups of male;  $\leq 15$  years = 27, 16-30 years = 69, 31-45 years = 162,  $\geq 46$  years = 126 and female; 3, 27, 54, 30 respectively) (b) and of Kamarhati (male; 18, 237, 192, 288 and female; 30, 156, 51, 45) for corresponding age groups.

The male patients of Indpur showed a significant increase of AFB score with their age increment; 1.48, 1.71 and 1.88 in 16-30, 31-45 and  $\geq 46$  years groups respectively compared to the score (0.94) of the  $\leq 15$  years group (Figure 2). But in Kamarhati, AFB score of all groups of both sexes ranges from 1.39 to 1.88. The score of  $\leq 15$  year's group of Kamarhati (1.43) is significantly higher (85%) than the corresponding male group of Indpur. Similarly, all female groups show a significantly greater AFB score than the corresponding group of Indpur.



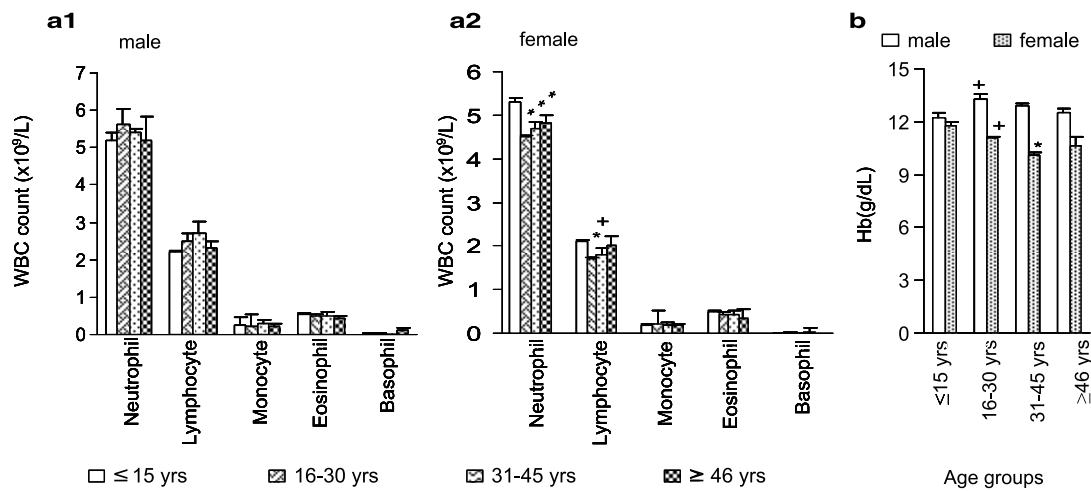
**Figure 2.** The AFB score of sputum smear of patients of Indpur (sample size of male;  $\leq 15$  years = 27, 16-30 years = 69, 31-45 years = 162,  $\geq 46$  years = 126 and female; 3, 27, 54, 30) (a) and Kamarhati (sample size of male; 18, 237, 192, 288 and female; 30, 156, 51, 45) respectively for corresponding age groups (b). Data represented in the figure are the mean  $\pm$  SEM. Significantly different from corresponding control. #P<0.01, \*P<0.001

Present results denote that mean annual income of 1+ scoring individual of Indpur is 18,000.00 INR/year, whereas these are 15,668.00; 11,170.00 and 9654.00 INR/year of 2+, 3+ and 4+ scoring individuals. The same for Kamarhati are 27,150.00; 31,340; 19,560; 13,240 INR/year respectively for the concerned groups (Figure 3a). The average incomes of last two AFB groups (3+ and 4+) of Indpur are significantly lower than the 1+ AFB group. This tendency is clearly observed in Kamarhati also. Data of Figure 3b suggest that in 'No addiction' group in Indpur, the AFB score is 1.18, whereas it is 1.74 (48% higher) in 'Smoking' group and 1.49 (27% higher) in 'Drinking' group. In 'Smoking + Drinking' group the score is 2.335 (98% higher). In Kamarhati, AFB score was 26% higher in 'Smoking' and 66% higher (p<0.001) in 'Smoking + Drinking' groups. The score of 'No addiction' group of Kamarhati was 20% higher than the similar group of Indpur.



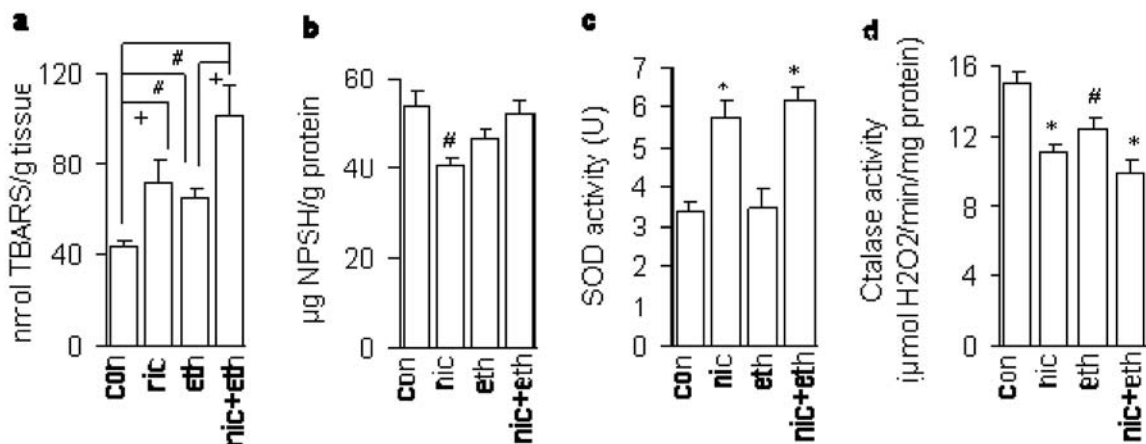
**Figure 3.** The impact of socioeconomic condition (income (INR)/year) on the AFB score of TB patients (210 out of 498 patients in Indpur and 698 out of 1017 of Kamarhati are in regular income. The sample size, n for different AFB scoring patients in Indpur; 1+ = 105, 2+ = 69, 3+ = 24, 4+ = 12 and in Kamarhati these are 315, 214, 107, 67 respectively (a). The Effect of drug addiction on the AFB score of 31-45 years age groups of male of both places (sample size n of Indpur; no addiction-40, smoking-34, drinking-29 and smoking + drinking-59 and similar groups in Kamarhati; 64, 39, 46, 43 respectively). The 31-45 age group is the major addicted group, and addiction in female is scarce (b). Data represented in the figure are the mean  $\pm$  SEM. Significantly different from corresponding control. +P<0.05, #P<0.01, \*P<0.001

Figure 4a1 demonstrates no variation in WBC count in normal males of different age groups of Indpur. Unlikely, the neutrophil counts in female are significantly lower (p<0.001) in all age groups with comparison to  $\leq 15$  years group. The lymphocyte count is also significantly lower in 16-30 years and 31-45 years age groups (Figure 4a2). A significantly higher hemoglobin value in male of 16-30 years group was observed whereas, the same is lower in 16-30 and 31-45 years groups of female than their corresponding youngest groups (Figure 4b).



**Figure 4.** Differential blood cell count of normal healthy male (a1) and female of Indpur block (a2), and their hemoglobin concentration (b) (sample sizes-n are as follows; male ≤15 years = 31, 16-30 years = 78, 31-45 years = 153, ≥46 years = 94 and female 68, 111, 165, 128 respectively. Data represented in the figure are the mean ± SEM. Significantly different from corresponding control. \*P<0.05, \*P<0.001

In Figure 5a, nicotine or ethanol alone or in combination increased MDA production in rat lung ( $p<0.05$  and  $p<0.01$ ). Nicotine significantly decreased NPSH content in lung (Figure 5b). Nicotine or nicotine +ethanol treatment significantly increased SOD activity by 79% (Figure 5c) whereas, catalase activity decreased in all three treatment groups (Figure 5d).



**Figure 5.** Effects of drug on concentrations of a) thiobarbituric acid (TBA) reactive substance- malondialdehyde (MDA) production, b) non-protein soluble thiol (NPSH), c) super oxide dismutase (SOD) and d) catalase activity in lung tissues of male Wister rats. (Sample size for any group n= 6). 'Con' stands for control, similarly 'nic' for nicotine and 'eth' for ethanol. Data represented in the figure are the mean ± SEM. Significantly different from corresponding control. \*P<0.05 #P<0.01, \*P<0.001.

## DISCUSSIONS

A proportionate increase in the number of male and female patients was observed in participants of different age groups in Indpur. In Kamarhati, the male patients of all the age groups showed a similar rate of occurrences (29-39%). But in female, the highest, 57.1% diagnosed belong to 16-30 year age group. Present results suggest that the disease sensitivity is in increasing order with increasing age in Indpur.<sup>24</sup> Possibly, decline in immuno-potency due to nutritional lacking augments age sensitivity.<sup>25</sup> The greater incidence of death in highest age group plausibly minimizes the number of sensitive individuals in this group. But, Kamarhati, an urban area shows similar type disease sensitivity. A certain part of Kamarhati belongs to Greater Calcutta (KMDA) which is highly populated condensed with several industries and large number of automobiles.<sup>11</sup> The age dependant disease sensitivity as found in Indpur is absent in Kamarhati.

The highest AFB scores from all age groups of Indpur are 1.88 in male and 1.39 in female (Figure 2a). This suggests that males are more sensitive. Sex dimorphic nature of this disease sensitivity has been reported earlier.<sup>26</sup> Results from the Figure 2 reveal that the lowest age group of both sex of Kamarhati is more affected than the corresponding groups of Indpur (1.43/1.79 Vs 0.94/0.96 for male and female respectively). Present results satisfy the Figure 1 data and indicate that possible environmental pollution could be the important factors for this.<sup>27</sup> In the 2001 census, Indpur had 51.4% males, 41.6% schedule caste and 9.5% schedule tribes.<sup>28</sup> Decadal growths for this period were 10.15% for Indpur, against 13.79% in Bankura district and which 40.13% was in West Bengal state.<sup>28</sup> On the other hand, Kamarhati had a 54% of male. It has an average literacy rate of 77%, higher than the national average of 59.5%, male literacy is 81%, and female literacy is 72%. The city has several industries of manufacturing of textiles, paints, articles of rubber, and products of jute.<sup>28</sup> In spite of the advantageous demographic profile and socioeconomic standard, lower age groups of Kamarhati are more affected than Indpur.<sup>29</sup> So, it may be hypothesized that man made unplanned changes in socio-demographic nature of an area may be more devastating than the natural adversity associated inchoate character of an area.

The economic status may be regarded as an important parameter of an individual's life style and health status.<sup>6,30</sup> India is an over-populated country with diversified economic strength, literacy and health/nutritional awareness.<sup>31</sup> Results from the present investigation suggest that the individuals of lower income groups are more vulnerable to TB (Figure 3a). Toxic effects of nicotine and alcohol on immune mechanisms and antioxidant systems have been reported earlier.<sup>32-34</sup> Our recent clinical data suggest that both drugs impart a devastating effect on TB which is additive in nature (Figure 3b). Interestingly, 'No addiction' group of Kamarhati showed 20% greater severity than the similar group of Indpur. This finding is also supported by the results of Figure 1 and Figure 2. Ironically, a better socioeconomic condition was not able to restrict disease severity in urban area (Figure 3a). Nutritional and health inequity is predominant in some of the parts of rural India.<sup>35-36</sup> Present data from Indpur show the impairment of hemoglobin content and WBC count in young undiagnosed female.

Present outcome of rat experiment indicates that nicotine is more toxic in terms of MDA production and NPSH depletion (Figure 5a and 5b) and MDA production is even greater at a co-treatment with ethanol. These results support the present clinical data showing the greater disease severity in drug addicted human individuals. Rat antioxidant enzymes have also been shown interfered after drug treatment.<sup>34</sup> Impairment of antioxidant profile consequences free radical mediated lung cell damage which may be associated with present clinical outcome.

In conclusion, the males are more sensitive which is furthered with drug usage especially in lower economic groups. In Indian context, drug addiction is not predominant in female but health and nutritional inequity is dominant as found in their lower immune and nutritional status.<sup>35-36</sup> There is no doubt that the demographic profile of Kamarhati is advantageous than Indpur. But unplanned urbanization with inadequate exhaust management may be more detrimental to disease sensitivity. In the present investigation, ethical norms on handling human subjects/ samples were maintained to our best possibilities. This is also important to mention the limitations of the present work is that, the specific differences in environmental, climatic and geographical nature of two areas and the possibilities of some individuals of having some other



preexisting disease conditions were not taken into account at the time of comparing the TB vulnerable. Though the present rat experiment was conducted in standard laboratory condition, still its results may suggest that damage in antioxidant systems might increase TB sensitivity. We strongly hope that our present findings could be helpful for further evaluation of influences of specific factors on the course of TB progression and its nature of severity.

## ACKNOWLEDGEMENT

All authors pass their humble regard to the health professionals of the concerned block hospitals and TB centers of Indpur and Kamarhati. They also offer their sincere thanks to all the participants and patients and wish a quality life to them.

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## KNOWLEDGE OF TUBERCULOSIS TREATMENT – A SURVEY AMONG TUBERCULOSIS PATIENTS IN (DOTS) PROGRAM IN NEPAL

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### ABSTRACT

**Introduction:** Tuberculosis (TB) has a long history. Its causative agent, *Mycobacterium tuberculosis*, may have killed more persons than any other microbial pathogen.

**Objective:** To find out patients knowledge about tuberculosis treatment.

**Method:** The study was carried out among the tuberculosis patients attended DOTS program in Nepal. Open ended self administered questionnaires based on the knowledge about Tuberculosis treatment were given to the survey population, literate group were asked to fill up the questionnaire and illiterate group were interviewed by a trained interviewer.

**Results:** This prospective study included 300 diagnosed cases of pulmonary tuberculosis. The age of the respondents varied from 11-70 years. Males were outnumbered than females. Perception about the tuberculosis has been changed positively with the intervention of chemotherapy, 83% of the respondents knew that tuberculosis is a curable disease. Majority of the tuberculosis patients were found to be conscious about duration of treatment 8 months or more than 8 months (82%). Regarding the method of treatment, majority of them suggested consultation with doctor (75%). Knowledge for consequences of incomplete treatment, 25% of respondents answered disease may attack again and only 7.3% of the patients were aware that incomplete treatment will develop drug resistant tuberculosis.

**Conclusion:** This survey showed that majority of patients knew that TB is a curable disease with regular treatment, duration of treatment and method of treatment. This will psychologically encourage them to abide by their treatment instructions. Patients' knowledge about consequences of incomplete treatment was poor. This study suggests that more emphasis should be given on teaching patients about consequences of incomplete treatment.

**Key words:** DOTS, *Mycobacterium tuberculosis*, Chemotherapy, Multi-drug resistant

### INTRODUCTION

World Health Organization (WHO), estimated that one third of the world's population has been exposed to the tuberculosis pathogen.<sup>1</sup> Globally, the rate of case

detection for new smear-positive cases reached 61% in 2006 (compared with the target of at least 70%) and the treatment success rate improved to 84.7% in 2005, just below the target of 85%.<sup>2</sup> Tuberculosis (TB) remains one of the major public health problems in Nepal. About 45% population is infected with TB, of which 60% are adult. Every year, 40,000 people develop active TB, of whom 20,000 have infectious pulmonary TB. Although introduction of DOTS has already reduced the numbers of deaths, however 5,000 to 7,000 people still continue to die each year.

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The review of National Tuberculosis programme (NTP) of Nepal was carried out jointly by Nepal Government and World Health Organization in 1994. The review team found the case finding result of 30% and the cure rate of only 40%. The review team recommended Nepal Government to change the NTP strategy to achieve better result. DOTS strategy was adopted in Nepal by approval of 5-year development plan in 1995. Impressive achievements have been made since then. The NTP has rapidly expanded the DOTS coverage from 1.7% in 1996 to 100% by July 2003. Now almost all diagnosed TB patients are getting treatment under DOTS strategy with more than 85% treatment success rate (now 88%).<sup>3</sup> Studies in different parts of the world revealed misconceptions and limited knowledge about the disease and its treatment.<sup>4,5</sup> The objective of this study was to determine tuberculosis patients knowledge about tuberculosis treatment.

## MATERIALS AND METHODS

The present prospective study was carried out in tuberculosis patients attended Directly Observed Treatment Short Course (DOTS) Programme in Kathmandu Medical College Sinamangal and GENTUP Nepal during January 2006 to December 2007. The study was conducted based on questionnaires included 300 diagnosed cases of pulmonary tuberculosis. A structured questionnaire prepared in English and translated into Nepali language was the tool for data collection. The research objective and methods were explained to the patients, and verbal consent was obtained from them before the data were collected. Random sampling method was used to select the target population for the survey. Open ended self administered questionnaires based on the knowledge about Tuberculosis treatment were given to the survey population, literate group were asked to fill up the questionnaire and illiterate group were interviewed by trained interviewer.

The questionnaire consisted of two sections: Section one, dealing with patient background characteristics (age and sex). Section two, knowledge about Tuberculosis treatment (Type of disease, duration of treatment, method of treatment, and consequences of incomplete treatment). The data collected by using structured questionnaire were entered into a

computer and data was analyzed by EPI-Info version 3.3.2, document version 8.08 updated Sept 2005 and presented by means of tables and diagrams.

## RESULTS

A total 300 tuberculosis patients were included in this prospective study. Background characteristics of respondents are shown in figure 1 and 2. The majority (73%) of the respondents belonged to 21-50 years age group shown in figure 1. Males constituted the majority (64%) of the interviewed patients shown in figure 2.

Respondent's general knowledge about TB treatment is shown in table 1, 2, 3 and figure 3. Regarding the type of disease majority (83%) of the respondents was aware that tuberculosis is curable disease (figure 3). Knowledge about duration of tuberculosis treatment, majority (82%) of them found to be conscious about duration of treatment 8 months or more than 8 months shown in table 1. Regarding consequences of incomplete treatment, only small number (7.3%) of the patients were aware that incomplete treatment will develop drug resistant tuberculosis shown in table 2. Knowledge on the method of treatment majority (75%) of them answered consultation with doctor shown in table 3.

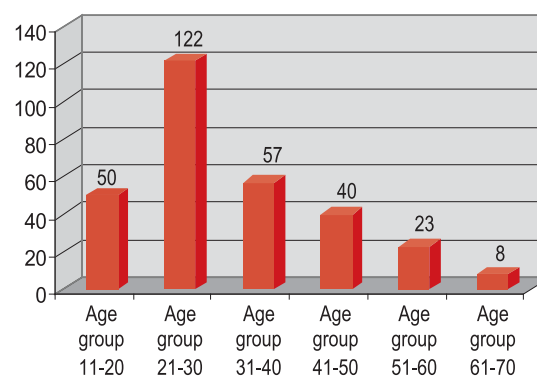


Fig. 1. Age wise distribution of patients

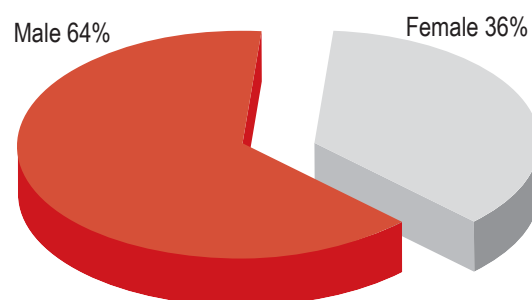


Fig. 2. Gender wise distribution of patients

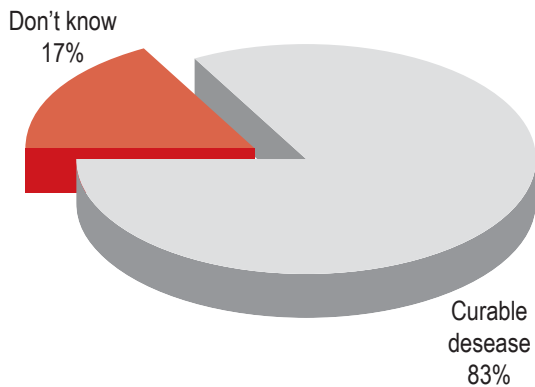


Fig. 3. Type of disease

**Table 1: People's knowledge about duration of treatment**

| Duration of treatment            | Frequency | %            |
|----------------------------------|-----------|--------------|
| 8 months                         | 192       | 64%          |
| 8-12 months                      | 54        | 18%          |
| According to doctor suggestion   | 8         | 2.6%         |
| Until disease is completely cure | 8         | 2.6%         |
| <b>Don't know</b>                | <b>38</b> | <b>12.6%</b> |

**Table 2: Consequences of incomplete treatment**

| Consequences of incomplete treatment    | Frequency | Percentage |
|---|-----------|------------|
| Disease may attack again                | 75        | 25%        |
| Disease will not be cured               | 53        | 17.6%      |
| Disease will worsen                     | 45        | 15%        |
| Disease will worsen and patient may die | 35        | 11.6%      |
| Person will die                         | 22        | 7.3%       |
| Develop drug resistant disease          | 22        | 7.3%       |
| Drug doses would be repeated            | 15        | 5%         |
| <b>Don't know</b>                       | <b>33</b> | <b>11%</b> |

**Table 3: Method of treatment**

| Method of treatment              | Frequency | Percentage   |
|----------------------------------|-----------|--------------|
| Doctor                           | 189       | 63%          |
| Doctor and take nutritional food | 35        | 11.6%        |
| Doctor or homeopathy             | 30        | 10.0%        |
| <b>Don't know</b>                | <b>46</b> | <b>15.3%</b> |

## DISCUSSION

The ultimate goal of patient education is to influence or change patients' health behaviors by providing them with information that motivates them to follow the treatment plan.<sup>6</sup> In case of tuberculosis (TB) different target groups which need to be addressed are patients, their relatives, health care providers and the community members.<sup>7</sup>

Until 50 years ago, there were no drugs to cure TB. Now, strains that are resistant to a single drug have been documented in every country surveyed and, what is more, strains of TB resistant to all major anti-TB drugs have emerged. Drug resistant TB is caused by inconsistent or partial treatment, when patients do not take all their drugs regularly for the

required period because they start to feel better, and doctors and health workers prescribe the wrong treatment regimens or the drug supply is unreliable. A particularly dangerous form of drug resistant TB is multi drug resistant TB (MDR-TB), which is defined as the disease due to TB bacilli resistant to at least isoniazid and rifampicin- the two most powerful anti-TB drugs. MDR-TB is rising at alarming rates in some countries, especially in the former Soviet Union, and threatens global TB control efforts.<sup>8</sup>

The finding of this study shows that majority of respondents (83%) knew that tuberculosis is a curable disease. The belief on curability is being increased with the intervention of DOTS. This reflects the increasing consciousness particularly among rural folk about the ailment. It is of great importance for the patients to

know that TB is curable with regular treatment, as this will psychologically encourage them to abide by their treatment instructions.

The analysis of the present investigation made it clear that majority (82%) of the patients knew the duration of the treatment and that the use of allopathic medicines is optimal method for treatment. Patients' knowledge about the duration of treatment need to cure the disease is an important educational message. As the bacteria needs 6-8 months for full clearance from host tissues.<sup>9</sup> This point is serious, as patients who did not know the total duration of treatment might at any stage of treatment stop taking the drugs. This interruption results in emergence of drug resistance to anti-TB drug. This result differs from the finding of a study conducted in India where by 64% of the respondents knew exactly the total duration of treatment.<sup>10</sup> However, the result is in agreement with the study in Iraq whereby 80.2% answered the disease is curable.<sup>11</sup>

Knowledge about consequences of incomplete treatment only small number 7.5% of respondents knew that incomplete treatment develop drug resistant tubercle bacilli. The results were in agreement with the reports of Subedi *et al.* (2004).<sup>12</sup> Where 5.8% were aware of the results of incomplete treatment. This finding suggests that the knowledge of consequences of incomplete treatment of the TB patients is poor. Above finding of this study suggests that more emphasis should be given on teaching patients about consequences of incomplete treatment. Early detection of drug resistance in TB allows starting of an appropriate treatment, which has an impact in the better control of the disease. MDR-tuberculosis constitutes a major threat to TB control. Patient compliance is a key factor in treatment success. In many countries, a significant proportion of patients stop treatment before completion, for various reasons. The premature interruption of treatment represents a problem for patients, their families and those who care for them, and those responsible for TB programmes.

## CONCLUSION

This survey showed that majority of patients knew that TB is a curable disease with regular treatment,

duration of treatment and method of treatment. This will psychologically encourage them to abide by their treatment instructions. Patients' knowledge about consequences of incomplete treatment is found poor. This study suggests that more emphasis should be given on teaching patients about consequences of incomplete treatment. Incomplete treatment of TB is worse than no treatment at all. When people fail to complete standard treatment regimens, they may remain infectious. The bacilli in their lungs may develop resistant to anti-TB drugs. People who infect will have the same drug resistant strain. While drug resistant TB is treatable, it requires extensively chemotherapy up to two years. It is expensive and more toxic to patient.

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## RETROSPECTIVE ANALYSIS OF USE OF EMPIRIC ANTI TUBERCULOSIS TREATMENT IN SMEAR NEGATIVE PULMONARY TUBERCULOSIS PATIENTS IN CENTRAL SRI LANKA

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### ABSTRACT

**Objective:** To critically analyze the outcome of sputum negative pulmonary TB patients who were managed in the Respiratory unit, Kandy Sri Lanka.

**Setting:** Respiratory Unit, Teaching hospital, Kandy.

**Method:** The subjects were between age 12 years or older and visited chest clinic Kandy, between January -December 2008 with a suspicion of pulmonary TB. 84 patients were reviewed with admission note, microbiology results and chest radiography. The characteristics of patients such as age, sex, clinical features, laboratory and radiographic findings were analyzed.

**Results:** The diagnosis of definite or probable smear negative pulmonary TB was made on treatment outcome at one month with ATT medication. At this endpoint, 67 (79.76%) had clinical and radiological improvement, 7(8.33%) had clinical improvement and 3 (3.57%) had radiological improvement. Mantoux test was positive in 46(78%) of definite cases and 6(85.7%) in probable cases. Mycobacterial culture was positive in 5 patients. 7 (8.3%) cases were diagnosed as 'non-TB' based on absence of clinical / radiological improvement or discovery of another cause at or before this study end point. In non TB group 3 had carcinoma, 2 had pneumoconiosis, 1 had bronchiectasis while in 1, cause was indeterminate. Mantoux became positive in 6 (83.3%) in non Tuberculosis group. There was no association between positive Mantoux and presence of active pulmonary TB.

**Conclusion:** Our findings suggest that empirical anti TB treatment is an acceptable practice if clinical suspicion of tuberculosis is high and patients show supportive radiological evidence of active TB.

**Keywords:** Smear negative pulmonary tuberculosis, empirical anti tubercular treatment

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### INTRODUCTION

Mycobacterium Tuberculosis (MTB) infects over one third of the world's population, causes 8 million new cases of disease, and over 2 million deaths every year worldwide.<sup>1</sup> Tuberculosis (TB) mainly affects people in the economically active age groups which results in an immense loss to communities and countries.

The WHO south East Asia region carries the highest burden of tuberculosis among all WHO regions.



Although Sri Lanka is not among the high burden countries, TB remains a widespread problem and poses a continuing threat to the health and development of the people in the country.<sup>2</sup>

Nearly 17000 people (80/100 000) are currently estimated to be suffering from tuberculosis. Every year, it's estimated that more than 11 000 new cases (60/100 000) arise. Over 50 000 people are expected to develop TB disease during next 5 years and out of this only half are expected to be smear positive TB cases.<sup>3</sup>

The confirmation of TB diagnosis is made by the detection of MTB bacilli. The detection of acid fast bacilli (AFB) on smear of respiratory specimen-sputum, induced sputum or bronchial washing, is essential for diagnosis of pulmonary TB.<sup>4</sup>

However sensitivity of the AFB smear result is known to be poor, varying between 30%-70% depending on the number of factors relating to how the test is being performed.

Although the culture of the tuberculosis bacilli is more sensitive (80%-85%), being able to detect as few as 10 bacteria per milliliter of sputum, it usually takes 3-6 weeks to receive culture results.

However considering the fact that nearly half of all patients with TB are smear negative, decision to start anti-TB treatment in patients with a high suspicion of TB can only be made on clinical scenario and typical radiological feature that not only benefits the patients, but also helps to control TB in the community.<sup>5,6</sup>

In Sri Lanka despite an effective national programme for tuberculosis control and mass scale immunoprophylaxis, tuberculosis still remains a growing public health issue with over 9000 new cases being detected annually.<sup>7</sup>

The empirical treatment of presumptive pulmonary TB is especially important in Sri Lanka where the prevalence of pulmonary TB is still high and only one third of the patients with pulmonary TB are sputum AFB smear positive.<sup>8,9,10</sup> The objective of this study was to critically analyze the outcome of sputum negative pulmonary TB patients who were managed in the chest clinic, Kandy.

## METHODOLOGY

We assessed the 84 patients who were registered as smear negative TB patients in chest clinic Kandy. The patients were of 12 years of age and above. The study was conducted over 12 month period January to December 2008.

These patients were retrospectively reviewed using the clinical records and chest radiographs. All of them had 3 negative sputum AFB smear results and started anti TB medication by individual physician's decision on the basis of symptoms and or radiographic features. All sputum smears were examined by trained microbiology technicians.

Medical records of these patients reviewed which included an admission note, microbiology results (smear and culture) and chest radiography interpretation. Data were collected using a questionnaire. We analyzed demographic characteristic of patients such as age and sex as well as clinical features including symptoms, laboratory and radiographic findings.

The patients were categorized as definite and probable cases depending on presence of both clinical and radiological improvement as evidence (definite) and only either one of it. (Probable)

## RESULTS

Eighty four patients who were treated as smear negative TB between January-December 2008 were analyzed. The mean age of the patient was 48 years with a male to female ratio was 61:39. Figure 1.

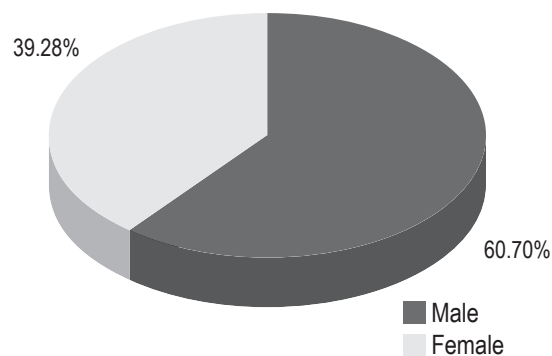


Fig. 1. Sex distribution of Study Population

The mean duration of treatment was 6 months 67 patients (79.76%) had both clinical and radiological improvement (definite cases), 7 patients (8.33%) had clinical improvement alone (probable cases) and 3 (3.57%) had radiological improvement alone (probable cases) figure 2.

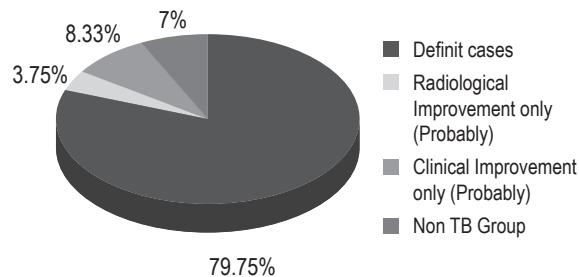


Fig. 2. Treatment outcome at 2 Months

Of the definite group 46 (78%) had strongly positive Mantoux test and in probable group it's 6 (85.7%). Figure 3.

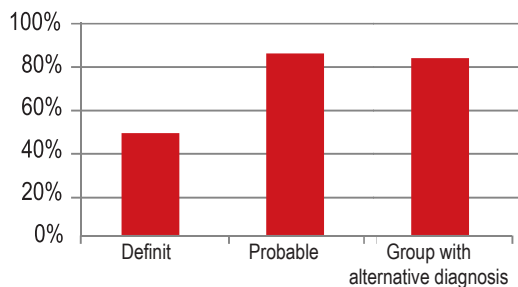


Fig: 3. Mantoux Positivity in Different Treatment

Confirmation of acid fast bacilli was subsequently obtained in 5 patients (7.4%) (all definite cases) from culture of initial pulmonary specimens. Seven patients (8.3%) were diagnosed as non TB based on absence of both clinical and radiological improvement or discovery of another cause for the pulmonary condition at or before this 2 month study end point. In non TB group 3 had carcinoma, Two patients had pneumoconiosis one had bronchiectasis while in 1 patient cause was indeterminate.

12 patients of this group showed adverse effects due to TB medication such as hepatitis, pruritis and however they were not so severe as to change or stop anti TB medications.

## DISCUSSION

The prompt initiation of treatment for pulmonary TB is the crucial factor which is responsible for controlling disease spread in the community. The fact that the smear negative but culture positive TB was responsible for the 17% of the TB transmission highlight the importance of initiation of anti TB medication in suspected cases of smear negative pulmonary TB at appropriate time.<sup>5,9</sup>

The definitive diagnosis of TB needs either confirmation by sputum positivity or culture positivity. However both these depend on various factors such as patient cooperation lab facility availability ,culture media availability etc. Although newer rapid diagnostic tools such as nucleic acid amplication method and serodiagnosis using ELISA have been introduced recently they are not yet considered as standard practice.<sup>4,6,7</sup>

In analysis of our study we found that decision to treat patients empirically with anti TB medications on selective basis is appropriate, as 91.63% showed improvement. (Both definite and probable group) But positive culture for AFB was noted only in 6.4% of this group which is far less than expected .This could be attributed to multiple factors related to patients and as well as technical problems associated with culturing AFB.<sup>11</sup>

However positivity of Mantoux test showed no significant difference among these two groups, as both these groups show more than 78% positivity. This fact needs further evaluation as we have to continue to follow up them further to see whether they too will develop TB or not.

There are no similar studies done in Sri Lanka to assess the outcome of patients who were treated as smear negative pulmonary TB. This study showed that use of appropriate criteria's to start treatment in selected groups (definite/probable) are worthwhile practice.

It should be taken in to consideration that these groups need very careful follow up in frequent intervals. One should look for clinical and radiological improvement in these selected groups and if there's no improvement there's need to look for possible drug resistant or secondary causes like connective tissue diseases , bronchial malignancy etc which can mimic pulmonary Tuberculosis.

### Limitations of this study

The short coming of this analysis was the fact we were unable to document clearly the criteria which were taken as clinical improvement and monitor these patients closely as this was retrospective study. In addition there were practical problems of collection, transport and culturing specimens. This may have contributed to poor outcome of culture results in this study.

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# PREVALENCE OF PULMONARY TUBERCULOSIS AMONG HIV INFECTED DRUG USERS IN POKHARA, KASKI, NEPAL

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## ABSTRACT

**Introduction:** Studies conducted in different countries suggest that HIV infected drug users have a higher chance of acquiring pulmonary tuberculosis (PTB) in comparison to general population. However, there is no information about the prevalence of PTB among HIV infected drug users in Nepal.

**Objectives:** The main objectives of this study were to document the socio-demographic and behavioral attributes; clinical symptoms and prevalence of PTB in HIV infected drug users in Pokhara, Kaski, Nepal.

**Methods:** In a cross-sectional study, we enrolled 62 HIV infected drug users not diagnosed with PTB in the past from five HIV care centers in Pokhara. Using questionnaire, first we documented participants' socio-demographic and behavioral attributes and clinical symptoms. This was followed by tuberculosis testing in all enrolled participants at the Regional Tuberculosis Center (RTC) in Pokhara.

**Results:** Of the 62 HIV infected drug users, PTB was diagnosed in 3 (4.8%) participants. All of them were male in the productive age group. Cough was the major clinical symptoms (54.8%) in the study participants. About 91.9% participants reported they had acquired HIV infection through injecting drug use. Buprenorphine/heroin was the major drug used (48.4%) for addiction.

**Conclusion:** This study provides first evidence of prevalence of PTB in HIV infected drug users in Nepal. The findings suggest tuberculosis testing be conducted in HIV infected persons including the HIV infected drug users in Nepal. Early detection of PTB in HIV infected drug users may help to reduce the morbidity and mortality as well as spread of TB in the community.

**Keywords:** Drug users, HIV/AIDS, Nepal, Pokhara, Tuberculosis

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## INTRODUCTION

Injecting drug users (IDUs) are at increased risk of acquiring and transmitting HIV infection primarily because of unsafe injection practices and high risk sexual behaviour.<sup>1</sup> Worldwide, the number of IDUs

is estimated at approximately 13.2 million. Over ten million (78%) IDUs live in developing countries (Eastern Europe and Central Asia, 3.1 million; South and South-east Asia, 3.3 million; East-Asia and Pacific, 2.3 million). HIV prevalence among drug users in many countries including Nepal has been estimated above 20%.<sup>2</sup> In 2007, the prevalence of HIV was 5.6% in Pokhara and 18.2% in Kathmandu.<sup>3,4</sup> However, the prevalence of PTB among HIV infected drug users is not known either in Pokhara or Kathmandu, Nepal.

HIV is a known risk factor for the development of tuberculosis in both the recently acquired tuberculosis infection as well as in latent TB cases.<sup>6</sup> Other known risk factors for TB include inadequate treatment, poverty, malnutrition, overcrowding, armed conflict and increasing number of displaced persons.<sup>7</sup> It is possible that the spread of TB in HIV infected drug users could be higher due to their behavioral characteristics such as poor adherence to therapy, nutritional factors and gathering including close contacts. Studies have shown that there is higher chance for the development of tuberculosis in drug users in comparison to general population of the community.<sup>8</sup> In many settings; the epidemic of IDUs has become intertwined with the HIV and the TB epidemics. Health systems have often responded with separate policies and structures to the detriment of the individual user and their communities.<sup>9</sup> Studies have shown that the leading causes of mortality in both HIV negative and positive IDUs are overdose, AIDS, tuberculosis and accident/trauma.<sup>10, 11</sup>

Till date studies conducted on TB/HIV co-epidemic in Nepal have been focused in hospital settings. No community based TB/HIV co-epidemic study has been conducted specifically targeting drug users.<sup>12,13,14,15</sup> So, this community based cross-sectional study was carried out in HIV infected drug users to investigate their socio-demographic, behavioral and clinical symptoms as well the prevalence of pulmonary tuberculosis in this particular population in Pokhara, Kaski.

## METHODOLOGY

This research was approved by Nepal Health Council and was carried out in the Western Regional TB Centre (RTC) between December 2006 and December 2007. Altogether 62 HIV infected

(both symptomatic and asymptomatic) drug users were recruited from: Friends of Hope (FOH), Ranipauwa; Community Support Group (CSG), Damside; Nauloghunti, New Road and Paluwa Srijana Chowk. The interviewer went to these centers to conduct interview and collect the sputum specimens of HIV positive subjects. Participants were selected by random sampling method using the patients' lists available in these centers.

After taking written informed consent, study participants were interviewed using questionnaire, which collected data on socio-demographic, behavioral and clinical features. Then, three sputa specimens (first spot, early morning, and second spot) were collected and transferred to Mycobacteria Research Laboratory at RTC, Pokhara. All three sputa specimen were processed for Acid Fast Bacilli staining using Ziehl Neelsen method.<sup>16</sup> In addition, early morning sputum were subjected to modified Petroff's method for decontamination and then inoculated into 2 sets of 3% Ogawa medium followed by incubation at 37°C for 6-8 weeks.<sup>17</sup> If the growth was obtained then colony morphology was studied, compared with standard positive control. All analysis (prevalence study) was performed using statistical package for social sciences (SPSS version 11.5).

## RESULT

Among 62 HIV infected drug users, 59 (95.2%) were males and 3 (4.8%) were females. The age group 21-30 year was predominant (54.8%) followed by 31-40 year (30.6%). Most of them had primary level education (51.6%), married (64.5%), unemployed (42.2%) and acquired HIV infection through IDUs (91.9%) as shown in table 1. Buprenorphine/heroin was reported to be the major drug used for addiction (48.4%) followed by Buprenorphine/heroin + Brown sugar (27.4%). Majority of the subjects were using drug for 1 to 3 times per day (64.5%). The most frequent time of drug use was in the morning (91.9%). Majority of the subjects (n=54) were using old/used needle (93.1%) with high rate of sharing (98.3) as shown in table 2.

Compared with female, more male participants reported they consumed alcohol (52.5 vs. 33.3%). In

contrast, more female than male participants reported they smoked tobacco (100 vs 88.1%). Cough was the major clinical symptoms (54.8%) followed by weight loss (40.3%) in all participants, as shown in table 5.

Among the 62 participants, 3 were co-infected with

TB of which all were culture positive and only one was both culture and sputum smear positive. Therefore, the overall prevalence of TB in HIV infected drug users was 4.8% (table 3). All the three co-infected patients were in their productive age that is between 21 and 40 years as shown in table 4.

| <b>Table 1: Socio-demographic characteristics of study participants by gender</b> |                            |                              |                             |
|---|----------------------------|------------------------------|-----------------------------|
| <b>Characteristics</b>  | <b>Male<br/>Number (%)</b> | <b>Female<br/>Number (%)</b> | <b>Total<br/>Number (%)</b> |
| <b>Age group (Yrs)</b>  |                            |                              |                             |
| 11-20   | 3(5.1)                     | 0                            | 3(4.8)                      |
| 21-30   | 31(52.5)                   | 3(100)                       | 34(54.8)                    |
| 31-40   | 19(32.2)                   | 0                            | 19(30.6)                    |
| 41-50   | 6(10.2)                    | 0                            | 6(9.7)                      |
| <b>Total</b>  | <b>59(100)</b>             | <b>3(100)</b>                | <b>62(100)</b>              |
| <b>Marital status</b>   |                            |                              |                             |
| Married   | 38(64.4)                   | 2(66.7)                      | 40(64.5)                    |
| Unmarried   | 16(27.1)                   | 1(33.3)                      | 17(27.4)                    |
| Divorced  | 5(8.5)                     | 0                            | 5(8.1)                      |
| <b>Total</b>  | <b>59(100)</b>             | <b>3(100)</b>                | <b>62(100)</b>              |
| <b>Education</b>  |                            |                              |                             |
| Illiterate  | 6(10.2)                    | 1(33.3)                      | 7(11.3)                     |
| Primary   | 18(30.5)                   | 1(33.3)                      | 19(30.6)                    |
| Secondary   | 31(52.5)                   | 1(33.3)                      | 32(51.6)                    |
| Higher Sec.   | 4(6.8)                     | 0                            | 4(6.5)                      |
| <b>Total</b>  | <b>59(100)</b>             | <b>3(100)</b>                | <b>62(100)</b>              |
| <b>Occupation</b>   |                            |                              |                             |
| Unemployed  | 25(42.4)                   | 3(100)                       | 28(42.2)                    |
| Businesses  | 11(18.6)                   | 0                            | 11(17.7)                    |
| Volunteer   | 9(15.3)                    | 0                            | 9(14.5)                     |
| Driver  | 4(6.8)                     | 0                            | 4(6.5)                      |
| Service   | 4(6.8)                     | 0                            | 4(6.5)                      |
| NGO/INGO  | 3(5.1)                     | 0                            | 3(4.8)                      |
| Plumber   | 1(1.7)                     | 0                            | 1(1.6)                      |
| <b>Total</b>  | <b>59(100)</b>             | <b>3(100)</b>                | <b>62(100)</b>              |
| <b>HIV transmission</b>   |                            |                              |                             |
| IDU   | 54(91.5)                   | 3(100.0)                     | 57(91.9)                    |
| Sexual  | 5(8.5)                     | 0                            | 5(8.1)                      |
| <b>Total</b>  | <b>100(100.0)</b>          | <b>50(100.0)</b>             | <b>150(100.0)</b>           |

| <b>Table 2: Behaviour characteristic of study participants</b> |                                       |                                   |                                    |                                    |
|--|---------------------------------------|-----------------------------------|------------------------------------|------------------------------------|
|  | <b>Features</b>                       | <b>Male (N=59)<br/>Number (%)</b> | <b>Female (N=3)<br/>Number (%)</b> | <b>Total (N=62)<br/>Number (%)</b> |
| <b>Alcohol addiction</b>                                       | Yes                                   | 31(52.5)                          | 1(33.3)                            | 32(51.6)                           |
| <b>Smoking habit</b>   | Yes                                   | 52(88.1)                          | 3(100)                             | 55(88.7)                           |
| <b>Drugs used</b>  | Buprenorphine/heroin                  | 27(45.8)                          | 3(100)                             | 30(48.4)                           |
|  | Buprenorphine/heroin +<br>Brown sugar | 17 (28.8)                         | 0                                  | 17(27.4)                           |
|  | Buprenorphine/heroin +<br>morphine    | 6(10.2)                           | 0                                  | 6(9.7)                             |
|  | Ganja                                 | 3(5.1)                            | 0                                  | 3(4.8)                             |
|  | morphine                              | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | Brown sugar                           | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | Nitroson                              | 2(3.4)                            | 0                                  | 2(3.2)                             |
| <b>Mode of drug use</b>  | IDU                                   | 35(59.3)                          | 3(100)                             | 38(61.3)                           |
|  | Both                                  | 20(33.9)                          | 0                                  | 20(32.3)                           |
|  | Oral                                  | 4(6.8)                            | 0                                  | 4(6.5)                             |
| <b>Frequency of use#</b>                                       | 3 times/day                           | 18(30.5)                          | 1(33.3)                            | 19(30.6)                           |
|  | 2 times/day                           | 12(20.3)                          | 0                                  | 12(19.4)                           |
|  | Once a day                            | 7(11.9)                           | 2(66.7)                            | 9(14.5)                            |
|  | 5 times/day                           | 7(11.9)                           | 0                                  | 7(11.3)                            |
|  | 4 times/day                           | 4(6.8)                            | 0                                  | 4(6.5)                             |
|  | 20 times/day                          | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | Once in a week                        | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | 25 times per day                      | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | 7 times per day                       | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | 15 times per day                      | 2(3.4)                            | 0                                  | 2(3.2)                             |
|  | 10 times per day                      | 1(1.7)                            | 0                                  | 1(1.6)                             |
| <b>Most frequent time<br/>of drug use</b>                      | Morning                               | 54(91.5)                          | 3(100)                             | 57(91.9)                           |
|  | Morning, evening and<br>day           | 3(5.1)                            | 0                                  | 3(4.8)                             |
|  | Day time                              | 2(3.4)                            | 0                                  | 2(3.2)                             |
| <b>Type of needle*</b>   | old/used                              | 51(92.7)                          | 3(100)                             | 54(93.1)                           |
|  | Disposable (Always)                   | 2(3.6)                            | 0                                  | 2(3.4)                             |
|  | Disposable (Sometime)                 | 2(3.6)                            | 0                                  | 2(3.4)                             |
| <b>Sharing of needle*</b>                                      | Yes                                   | 54(98.2)                          | 3(100)                             | 57(98.3)                           |
|  | No                                    | 1(1.8)                            | 0                                  | 1(1.7)                             |

\*4 cases are oral drug user and hence analysis is done for only 58 cases.

# In IDUs cases, frequency of use is equivalent to the number of syringes per day.

**Table 3: Distribution of study participants by TB status and sex**

| TB status    | Sex                |                      | Total<br>Number (%) |
|--------------|--------------------|----------------------|---------------------|
|              | Male<br>Number (%) | Female<br>Number (%) |                     |
| Yes          | 3 (5.1)            | 0                    | 3 (4.8)             |
| No           | 56(94.9)           | 3 (100)              | 59 (95.2)           |
| <b>Total</b> | <b>59 (100)</b>    | <b>3 (100)</b>       | <b>62(100)</b>      |

**Table 4: Distribution of the study participants by TB status and age group**

| Age group (in yrs) | TB status of patients |                  | Total<br>Number (%) |
|--------------------|-----------------------|------------------|---------------------|
|                    | Yes<br>Number (%)     | No<br>Number (%) |                     |
| 11-20              | 0                     | 3(5.1)           | 3(4.8)              |
| 21-30              | 2(66.7)               | 32(54.2)         | 34(54.8)            |
| 31-40              | 1(33.3)               | 18(30.5)         | 19(30.6)            |
| 41-50              | 0                     | 6(10.2)          | 6(9.7)              |
| <b>Total</b>       | <b>3(100)</b>         | <b>59(100)</b>   | <b>62(100)</b>      |

**Table 5: Distribution of clinical signs and symptoms among study participants**

| Clinical features | Male (N=59) | Female (N=3) | Total<br>Number (%) |
|-------------------|-------------|--------------|---------------------|
|                   | Number (%)  | Number (%)   |                     |
| Cough             | 31(52.5)    | 3(100)       | 34(54.8)            |
| Weight loss       | 23(39.0)    | 2(66.7)      | 25(40.3)            |
| Chest pain        | 23(39.0)    | 1(33.3)      | 24 (38.7)           |
| Fever             | 20(33.9)    | 2(66.7)      | 22(35.5)            |
| Loss of weight    | 19 (32.2)   | 1(33.3)      | 20(32.3)            |
| Diarrhoea         | 13(22.0)    | 1(33.3)      | 14(22.6)            |
| Night sweat       | 12(20.3)    | 0            | 12(19.4)            |
| Haemoptysis       | 4(6.8)      | 1(33.3)      | 5(8.1)              |

## DISCUSSION

The results of this study show that prevalence of PTB is 4.8% in HIV infected drug users in Pokhara, Nepal. On ethical ground all diagnosed pulmonary TB cases in our study were put under anti-TB treatment under DOTS strategy of NTP Nepal.

Several studies conducted in the past have suggested higher prevalence of PTB in HIV infected persons. For example, on PTB surveillance among HIV infected persons in Cambodia; authors have documented 9% of participants with active TB.<sup>18</sup> Similarly, in the study carried out by Montefiore Medical Center, New

York, authors have documented the TB incidence rate among anergic, HIV sero-positive subjects as 6.6 cases per 100 person- years.<sup>19</sup> A study conducted in South India (Chennai ) has shown TB prevalence among HIV positive IDUS as 33.9%, which is much higher than what we have reported in our study.<sup>20</sup> A study carried out in drug users, registered at the Indian Council of Medical Research Unit in northeastern states of India has demonstrated TB as the most common opportunistic infection (12.5% for pulmonary TB and 6.7% for extra-pulmonary TB) in HIV infected drug users.<sup>21</sup>

In terms of the drug users' behavioral characteristics, our findings show that IDU constitute the significant



proportion of drug users with higher rate of unsafe needle sharing. A study conducted among drug users in Pokhara has revealed similar result.<sup>22</sup>

Our study has demonstrated that cough is the major clinical symptom of HIV infected drug users. A study conducted at the department of Microbiology, King's College London has documented prevalence of cough in 83.6% of HIV infected drug users, which is about one and half times higher than what we have reported in our study.<sup>23</sup> Similar findings have been reported by Cain et al, where authors have documented cough, weight loss and fever in more than 50% of participants.<sup>24</sup>

However, we cannot ignore several limitations in this report. Among other one important limitation of this study is its small sample size. Thus, findings of our study need to be validated by conducting similar studies with larger sample size in other parts of the country.

## CONCLUSION

The success of tuberculosis control program depends on the early detection and complete treatment of the tuberculosis disease. In conclusion, our study provides first evidence of prevalence of PTB in HIV infected drug users in Nepal. Our findings suggest that there is a need of joint TB/HIV coordination programme for the early diagnosis and treatment of tuberculosis in the high risk group like HIV infected drug users. We recommend that NTP Nepal should initiate the early diagnosis of PTB among high risk group like this even through culture for TB bacilli as sputum microscopy may not detect TB bacilli in such cases.

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the anticipation of early treatment if diagnosed with tuberculosis.

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Case Report

## ROLE OF LOW-LEVEL NITROGEN LASER THERAPY IN TUBERCULAR COLD ABSCESS NOT RESPONDING TO SURGERY & CHEMOTHERAPY A SERIES OF CASE REPORT

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### ABSTRACT

**Background:** Tubercular empyema is one of the commonest chronic diseases in the developing countries of the world including India. As the problem of drug resistant strain of *tubercular bacilli* is increasing, new modalities of treatment that could act against resistant strain are needed.

**Objective:** The purpose of this study was to evaluate the efficacy of low-level nitrogen laser therapy (LLLTL) as an adjuvant to anti-tubercular treatment in case of tubercular empyema that was not responding to conventional anti-tuberculosis drugs and repeated pus aspiration.

**Patient:** The patient, a 19 year old male was diagnosed with tubercular empyema. He was not improving by conventional treatment and pus aspiration. The patient was administered intralesional nitrogen laser (337 nanometer, average power 5 mW) for 780 seconds at intervals of 72 hours up to 10 weeks.

**Results:** After the fifth laser irradiation session, decrease in chest pain was reported and pus mixed with blood pleural fluid aspirated. After the tenth laser irradiation session, serous pleural fluid was aspirated. After 20 sessions of laser irradiation the empyema was healed completely and the patient also regained almost complete expansion of lung.

**Conclusion :** LLLTL was observed to results in the healing of the tubercular empyema and also found to make the empyema free of *Mycobacterium tuberculosis*. However, further randomized studies with more patients are needed to prove the efficacy of this method.

**Key words:** -*Mycobacterium tuberculosis*, empyema, laser

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### INTRODUCTION

Tuberculous empyema presents a more difficult problem, since the lung and pleura are usually involved with irreversible pathological changes which make expansion and proper functioning of the lung impossible. However, it appeared theoretically possible that if tuberculous empyema were treated at an early stage, before irreversible changes took place that a cure might be obtained.

This report deals with the successful treatment of a patient with tuberculous empyema by use of low level laser therapy.

## CASE REPORT

A 19-year-old male, was admitted on February 2008 with two weeks history of high grade fever, dry cough and left sided chest pain. Patient had been treated for sputum positive pulmonary tuberculosis from April 2007 to October 2007. History of contact with known tuberculous patient was positive. He had received Isoniazid (INH) 600 mg, Rifampicin (RIF) 600mg, Ethambutol (EMB) 1200 mg, Pyrazinamide (PZA) 1500 mg Directly Observed Treatment, Short course (DOTS Category-I).

On general examination, he was cachectic, febrile, trachea shifted towards right side. Systemic examination revealed dull percussion on left side of chest. Auscultation of chest revealed breath sound absent in left chest.

A full blood examination showed Haemoglobin of 11.6gm%, white cell count 12,700, Erythrocytes Sedimentation Rate of 30mm at the end of 1<sup>st</sup> hour. Blood sugar, urea, creatinine were normal. Human Immunodeficiency Virus, T- cell interferons were negative and Tubercular antibody were positive. Thick pus from pleural cavity showed acid-fast bacilli (AFB) in Ziehl Neelsen (ZN) staining. Culture on Lowen stein – Jensen slopes(L-J) was negative but Deoxyribo Nucleic Acid testing for *Mycobacterium tuberculosis* amplified using the polymerase chain reaction (PCR) was positive. Sputum for acid-fast bacilli was negative on ZN staining. Culture of sputum on L-J slopes was negative. Culture for pyogenic organisms was negative. X-ray of chest revealed homogenous opacity left side of chest with shifting of the mediastinum towards right side (Figure-1).

After confirmation of the diagnosis, patient was put on DOTS category –II along with repeated aspiration because patient was not ready for intercostal tube drainage. In spite of this treatment for 2 months, amount of pleural fluid was increasing radiologically and patient deteriorated clinically.

The study has been approved by institutional review board. After obtaining the informed consent, we gave



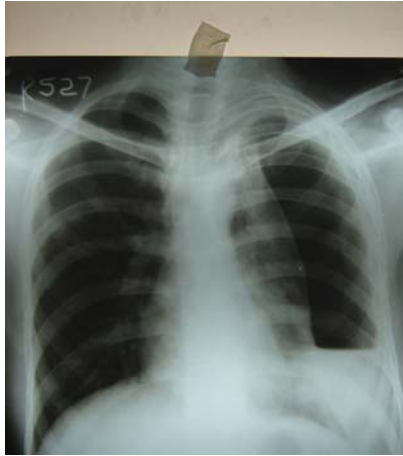
Fig. 1: X-ray of chest showing homogenous opacity left side of chest with shifting of mediastinum to right side.

intrapleural laser therapy along with continuation of DOTS category-II. The intrapleural laser therapy required local anesthesia. The nitrogen laser used in this study (wave length 337 nm, energy 300 microjoules and an average power output of 5 mW at the tip of the fiber) was manufactured by Raja Ramanna Center for Advanced Technology, Indore, India.

The empyema was exposed to nitrogen laser irradiation for 780 seconds at 72 hours interval for total 20 sitting. For laser irradiation the sterilized jalco canula (16 Gauge, 50 mm length) was introduced inside the pleural cavity and after aspiration of fluid from pleural cavity, the optical fiber of the laser equipment was introduced into the pleural cavity. At each session whole of the plural cavity was irradiated.

After the fifth laser irradiation session, decrease in chest pain was reported and pleural fluid aspiration became pus mixed with blood. After the tenth laser irradiation session, serous pleural fluid aspirated. After 20 sessions of laser irradiation the empyema was healed completely, PCR for M.TB complex negative and the patient also regained almost complete expansion of lung. Follow-up x-rays of chest revealed resolution of empyema on left side of chest and complete expansion of left lung (Figure-2 and 3).

Patient develops left sided mild pneumothorax after two months of stopping treatment which was managed conservatively. There was no recurrence of disease during 2 years of follow up.



**Fig. 2:** X-ray of chest showing left sided hydropneumothorax



**Fig. 3** X-ray of chest showing complete resolution of empyema



**Fig-4** X-ray of chest showing left sided mild pneumothorax

## DISCUSSION

This study was motivated by the encouraging results obtained earlier by us on the use of low level nitrogen laser therapy in chronic pulmonary tuberculosis

non-responding tubercular lymphadenopathy and sinus.<sup>1,2,3</sup> Results of the case study showed that patient who had received antitubercular treatment 2 months and had been aspirated showing no response to the therapy responded to intrapleural nitrogen laser irradiation. The exact mechanism of therapy by nitrogen laser irradiation is not clearly understood. The high intensity focused nitrogen laser irradiation has been shown to lead to direct inhibition of bacteria.<sup>4</sup> Even low intensity nitrogen laser irradiation has been shown to result in significant changes in fluidity of lipid regions in cell wall of laser-exposed cells which could affect infectivity of *mycobacterium tuberculosis* in the host.<sup>5</sup> Experiments also suggest that nitrogen laser irradiation can influence the immune response. For example nitrogen laser irradiation was observed to enhance the intracellular killing of internalized bacteria in human neutrophils.<sup>6</sup> However; more work is required for a more clear understanding of the mechanisms involved in the observed therapeutic effect of nitrogen laser irradiation.

## SUMMARY

A patient with tuberculous empyema and non-expandable lung was treated by the intra pleural low level laser therapy. LLLT resulted in prompt expansion of the lung and disappearance of the empyema. The LLLT may be specific in the treatment of tuberculous empyema when used before irreversible pathological changes have taken place.

## CONCLUSION

Nitrogen laser irradiation was observed to result in the healing of the tubercular empyema which was not responding to conventional antitubercular and pus aspiration. The laser irradiation was also found to make the fluid free of *mycobacterium tuberculosis*. Further randomized studies with more patients are therefore, desirable to establish this mode of therapy for the treatment of tubercular empyema.

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**Case Report**

## **A RARE CASE OF BREAST TUBERCULOSIS - REPORT AND LITERATURE REVIEW**

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### **ABSTRACT**

Isolated Tuberculosis of Breast is uncommon, even in developing countries where pulmonary and other extrapulmonary manifestations are endemic. The significance of Breast tuberculosis is due to rare occurrence and mistaken identity with breast cancer and pyogenic breast abscess. Breast Tuberculosis has no defined clinical features. Radiological imaging is not diagnostic. The main sign and symptoms of this patient included a painful tender lump in the breast. The diagnosis was confirmed by Fine Needle Aspiration Cytology. Anti Tubercular Treatment was the therapeutic main stay. Surgical intervention was reserved for aspiration of cold abscess and excision of residual sinuses and masses.

### **INTRODUCTION**

Tuberculosis of Breast is seen rarely. Over the years since the first description of tubercular mastitis in 1929, the incidence, clinical presentation, diagnostic and treatment methodology of Breast tuberculosis has gradually changed. Breast Tuberculosis is rare in western countries. Incidence being less than 0.1% of the Breast lesions examined histologically. But, with global spread of AIDS, mammary tuberculosis may no longer be uncommon in developed world.<sup>1</sup> The incidence of Tuberculosis in general is still quite high in India and so is expected of the breast tuberculosis. But the disease is often overlooked.<sup>1</sup> Extra-pulmonary TB can be effectively treated with short-course chemotherapy, often with fewer drugs than in the case of pulmonary TB. Except for meningitis, all other forms of extra-pulmonary TB can be successfully treated with 6-month regimens.

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### **CASE REPORT**

A 23 year old woman presented with complaints of lump in her right breast which appeared since one month and gradually increased in size. Her medical history was unremarkable. On inspection there was no visible discrete swelling in the right breast and no erythema was present. Physical examination revealed a lump of 4x2 cms, firm with restricted mobility in the upper outer quadrant. It was tender. Nipple retraction and nipple discharge was not seen. On examination there was no axillary lymphadenopathy. A diagnosis of pyogenic abscess was made initially and was treated with empirical with Amoxicillin with clavulanic acid for 7 days. Mammogram was not done initially as it was very painful mass. After one week, patient reported with FNAC report confirming diagnosis of tuberculosis of breast. She was started on a course of Antitubercular Therapy.

On the follow up clinical examination after two months of treatment the lump in the breast had regressed in size. The diagnosis of Tuberculosis of Breast was based on strong suspicion of tuberculosis on both clinical and histological grounds, together with a prompt response to anti-tuberculous treatment.

She was continued with Anti-tubercular Therapy for remaining 4 months on category 1 regimen and reviewed in OPD regularly

**Laboratory** findings were within normal limits except leucocytosis. Hb%-11 gms/dl, Total WBC Count-11,900cells/cmm, Differential count-Neutrophils-79%, Lymphocytes - 18%, Eosinophils - 02% Monocytes - 01%, Basophils - 00%, ESR - 62mm/hr.

Chest x ray showed no evidence of active or healed tuberculous lesion in the lungs.

**Mantoux Test** – after 48 hrs Induration-present, 20x28mm positive **ZN stain of the smear** was negative and **Acid fast bacilli** (AFB) culture was also negative. **Gram Stain** of the material did not reveal any micro-organisms, aerobic and anaerobic culture of the caseous material did not yield any pyogenic micro-organisms after 10 days incubation.

**Serology:** HIV- Negative, HBsAg - Negative

**Ultrasonography** shows multiple ill-defined hypo echoic areas noted in the outer periaareolar area measuring around 30x16mm. The lesion involved the subcutaneous area and fatty tissues. No calcifications seen. No obvious increase in vascularity noted. No obvious clear collection noted.

Rest of the right breast parenchyma appeared normal. Axillary tail appeared normal. No obvious axillary lymph nodes seen. Left Breast: Left breast parenchyma appeared normal. Final impression: Features are suggestive of focal necrotic changes in right breast.

**Fine needle aspiration cytology** revealed epitheloid cells granulomata, with caseous necrosis. Impression– cold abscess.

## DISCUSSION

First case of Tuberculosis Breast was first described by Sir Asley Cooper in 1829 as scrufulous swelling of the bosom.<sup>1</sup> Tuberculous involvement of the breast is rare and mostly from extramammary tuberculous

lesion. Since its first description in 1829<sup>3</sup>, over 700 cases have been reported.<sup>5</sup>

Breast tuberculosis is a rare disease although its incidence ranges between 0.1% to 0.52%, it increases in endemic regions.<sup>2</sup> Tuberculosis of breast is classified as primary if there is no other organ involved and secondary when a source outside breast can be identified. The mode of spread to the breast may be haematogenous, lymphatic, direct extension from chest wall (pleura or ribs) or the axillary nodes and by inoculation of broken skin or duct opening by infected sputum.<sup>3</sup> In our case breast tuberculosis was considered to be the primary form because another tuberculosis infection focus was not detected by physical examination or radiological examination and there was no prior history. However, Vassilakos stated that primary breast tuberculosis was probably quite rare and was diagnosed because the clinician was unable to detect the true focus of the disease. Later on, breast tuberculosis was considered invariably secondary to a lesion elsewhere in the body.

Tuberculosis of breast commonly affects women in their reproductive age group between 21yrs- 30yrs, which is also seen in this case. This may be because the female breast undergoes frequent changes during the period of activity and is more liable to trauma and infection.<sup>1</sup>

Breast tuberculosis most commonly presents as a lump in the central or upper outer quadrant of the breast. It is probably due to frequent extension of tuberculosis from axillary nodes to the breast. Multiple lumps are less frequent.<sup>1</sup> According to the Cooper's theory, communication between the axillary glands and the breast results in secondary involvement of the breast by retrograde lymphatic extension. Supporting this hypothesis was the fact that axillary node involvement was shown to occur in 50 to 75 per cent of cases of tubercular mastitis<sup>1</sup>. In our case ipsilateral axillary nodal involvement was not present on clinical and radiological evaluation.

It can also present as breast abscess, especially in young women. In a review of benign breast diseases in India, Shukla and Kumar found Tubercular breast



abscess to be a common presentation of breast tuberculosis.<sup>1</sup>

Breast Tuberculosis is most misdiagnosed and patient is often subjected to numerous investigations before definitive diagnosis is made.

**Mantoux test** usually is positive in adults in endemic area for tuberculosis. It is of no diagnostic value for breast tuberculosis. **Chest x ray** may show evidence of active or healed tubercular lesion of lungs, in few cases may reveal clusted calcification in axilla suggesting the possibility of lymph node tuberculosis.<sup>1</sup>

**Mammogram** in breast tuberculosis is of limited value. However Breast tuberculosis is found in young women of 20-40years of age, dense breast makes interpretation of mammogram difficult. Moreover this facility may not be available in less developed world where disease is common. **Ultrasonography** of breast is cheap, easily accessible and helps in characterizing the lesion better (especially cystic from solid lesion) without exposure of radiation.<sup>1</sup>

**C T scan** seldom adds to diagnostic yield other than in defining the involment of thoracic wall MRI of Breast again finding are nonspecific. **Fine needle aspiration cytology** from breast lesion continues to remain an important diagnostic tool of Breast tuberculosis. Approximately 73% cases of Breast tuberculosis can be diagnosed on FNAC when both epitheloid cell granuloma and necrosis are present. Biopsy of the abscess wall and demonstration of characteristic histological features or culture are essential to confirm the diagnosis of Breast tuberculosis.

Though **Mycobacterial culture** remains the gold standard for diagnosis of tuberculosis, the time required and frequent negative results in paucibaccillary specimens are important limitations. Moreover, culture is not always helpful in the diagnosis of Breast tuberculosis. **Polymerase chain reaction** mostly used as a tool to distinguish tubercular mastitis from other granulomatous mastitis. PCR is by no means absolute in diagnosing tubercular infection and false negative reports are still a possibilities.<sup>1</sup>

**Histopathology of specimen** finding include epitheloid cell granuloma with caseous necrosis in

the specimen. Breast tuberculosis and carcinoma occasionally co-exist hence high index of suspicion is necessary.<sup>1</sup>

ATT is the backbone of treatment of Breast tuberculosis. The treatment of breast tuberculosis consists of anti-tubercular chemotherapy (ATT) and surgery with specific indications. No specific guidelines are available for the chemotherapy of breast tuberculosis *per se*. The regimen generally followed in the treatment of breast tuberculosis is similar to that used in pulmonary tuberculosis.



A picture of breast after completion of ATT

The Revised National Tuberculosis Control Programme (RNTCP) of India recommends category III regimen (2HRZ/4HR) for less serious forms of extra-pulmonary tuberculosis. The World Health Organization has recommended a 4-drug intensive phase (2EHRZ) in category III regimen as well.<sup>1</sup>

Mutilating surgery like simple mastectomy for breast tuberculosis was in vogue in the past with the belief that the lesion tends to persist and reappear with Conservative treatment even with chemotherapy.<sup>7</sup> Residual lump following ATT may require surgical removal. Simple mastectomy with or without axillary clearance is rarely required.<sup>1</sup>

## CONCLUSION

Extra-pulmonary tuberculosis occurring in the breast is extremely rare. It warrants a high index of suspicion on clinical examination and pathological or Microbiological confirmation of all suspected lesion. Breast tuberculosis is uncommon even in countries where the incidence of pulmonary and extra-pulmonary tuberculosis is high. In the absence

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of well-defined clinical features, the true nature of the disease remains obscure and it is often mistaken for carcinoma or pyogenic breast abscess. It also presents a diagnostic problem on radiological and microbiological investigations and thus high index of suspicion acquires an important position. The disease is eminently curable with the modern anti-tubercular chemotherapeutic drugs with surgery playing a role in the background only.

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**Case Series: Original Article**

## TUBERCULOSIS AND DIABETES MELLITUS: A Case Series of 100 Patients

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### ABSTRACT

**Introduction:** Tuberculosis and Diabetes mellitus are two public health problems which not only often coexist but have serious implications on each other. DM has an impact on symptomatology, radiological presentation, diagnosis and management of TB. TB has a significant impact on DM, causing unmasking of DM and poor control because of stress or because of drug treatment for TB. Present study attempts to assess this coexistence with regard to the age predisposition, sex preponderance, duration and glycemic control of diabetes and the radiological presentations.

**Materials and Methods:** 100 patients presenting to the Department of Tuberculosis and Chest Diseases, Government Medical College, Patiala, who were suffering from both Tuberculosis and Diabetes Mellitus, were studied. Various parameters considered included age, sex, history of diabetes with regard to the duration and the glycemic control and the radiological presentations.

**Results:** It was found that majority were males (61/100). The age group most commonly involved was the 40-60 year group (76/100). Majority had their Diabetes diagnosed before the diagnosis of Tuberculosis (57/100), 23 had diagnosis after TB diagnosis, and 20 simultaneously with TB diagnosis. Out of these 57 diagnosed diabetics, 11 patients had controlled diabetes whereas 46 (87.1%) had uncontrolled diabetes. 32 patients had the typical radiological lesions while 68 had atypical presentations with either lower lobe involvement, multi lobe involvement, cavitations or shadows fanning out from the hilum.

**Conclusion:** TB and DM often coexist together and adversely effect each other. Both need to be managed properly in order to achieve favorable treatment outcome.

**Key Words:** TB, DM

### INTRODUCTION

Incidence of tuberculosis is greatest among those with conditions impairing immunity<sup>1</sup>, such as human immunodeficiency virus (HIV) infection and diabetes.

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Diabetes mellitus significantly contributes to the burden of incident TB cases. In a study in India, DM accounted for 14.8% of pulmonary TB and 20.2% of smear positive TB.<sup>2</sup> It has also been postulated that transitory changes in carbohydrate metabolism in patients with DM may lead to persistent hyperglycemia, increasing the chances of development of TB. The global burden of diabetes is increasing, and recent estimates highlight the importance of this disease in India. There were an estimated 20–30 million people in India with diabetes in 2000 (estimates vary with study methodology)<sup>3,4</sup>, and projections suggest prevalence will rise to almost 80 million people by 2030. The

co existence of these two conditions has serious implications with regards to the clinical presentations and radiological findings, the management and the final treatment outcomes.<sup>4</sup>

Present study attempts to assess this coexistence with regard to the age predisposition, sex preponderance, duration and glycemic control of diabetes and the radiological presentations.

## MATERIALS AND METHODS

100 patients presenting to the Department of Tuberculosis and Chest Diseases, Government Medical College, Patiala, who were suffering from both Tuberculosis and Diabetes Mellitus, were studied. Various parameters considered included age, sex, history of diabetes with regard to the duration and the glycemic control and the radiological presentations.

## RESULTS

It was found that majority were males (61/100). The age group most commonly involved was the 40-60year group (76/100).

| Diabetes before TB | Diabetes with TB | TB before Diabetes |
|--------------------|------------------|--------------------|
| 57 (57%)           | 20 (20%)         | 23 (23%)           |

Majority had their Diabetes diagnosed before the diagnosis of Tuberculosis (57/100), 23 had diagnosis after TB diagnosis, and 20 simultaneously with TB diagnosis.

| Regular treatment and Controlled DM with TB | Irregular OHA's and Uncontrolled DM with TB | Alternate system of Medication and Uncontrolled DM with TB | Regular treatment and Uncontrolled DM with TB |
|---|---|--|---|
| 11(19.3%)                                   | 34 (59.6%)                                  | 3 (5.3%)   | 9 (15.8%)                                     |

Out of these 57 diagnosed diabetics, 11 patients had controlled diabetes whereas 46 (87.1%) had uncontrolled diabetes. Out of these, 34 were on oral irregular hypoglycemic, 3 on alternate system of medicine and 9, despite of having regular medication, had uncontrolled diabetes.

| Typical radiological features | Atypical radiological features |                        |                        |                 |
|-------------------------------|--------------------------------|------------------------|------------------------|-----------------|
| 32 (32%)                      | 68 (68%)                       |                        |                        |                 |
|                               | Fanning out from hilum         | Lower lobe involvement | Pneumonia like picture | Any combination |
|                               | 11 (16.2%)                     | 32 (47.1%)             | 7 (10.3%)              | 18 (26.4%)      |

32 patients had the typical radiological lesions while 68 had atypical presentations with either lower lobe involvement, multi lobe involvement, cavitations or shadows fanning out from the hilum.

## DISCUSSION

The association of Tuberculosis and Diabetes has been studied since long. In 1964, Richard Morton's *Phthisiologia: or a treatise on consumption* stated the association even in Roman times. In the latter half of the 19<sup>th</sup> century, Root stated that the diabetic patient appeared doomed to die of pulmonary TB if he succeeded in escaping coma. Half a century ago, expert clinics were established for "tuberculous diabetics".<sup>5</sup>

TB is a stressful condition which can worsen the diabetes and can lead to the higher requirement of the anti diabetic agents. As per the correlation between the ventilation and perfusion, since the perfusion is more in the middle and lower lobes, TB bacilli find a more congenial environment for the growth in the glucose rich blood in uncontrolled diabetics.

Present study attempts to assess this coexistence with regard to the age predisposition, sex preponderance, duration and glycemic control of diabetes and the radiological presentations.

Diabetes mellitus has been found to be associated with progressive shift of male predominance in pulmonary tuberculosis.<sup>6</sup> Yamagishi *et al.*, also found a male predominance among 352 tuberculosis patients with diabetes.<sup>7</sup> Similar were the findings from our study showing male predominance (61/100). Although the cause of this discrepancy is unclear, it is possible that genetic or socio-cultural differences among the populations might affect the way in which diabetes mellitus influences the gender distribution in pulmonary tuberculosis.

Swai *et al* prospectively followed 1250 African patients with Diabetes mellitus for several years. In 25.7%, Tuberculosis was diagnosed prior to onset of Diabetes mellitus, and in 45.7%, subsequently. In 20.6%, Tuberculosis and Diabetes were diagnosed simultaneously.<sup>8</sup> Our study was comparable to this study with majority of the patients having their Diabetes diagnosed before the diagnosis of Tuberculosis (57/100), 23 diagnosed after TB diagnosis, and 20 with TB diagnosis.

Prevalence of Tuberculosis was greater in those with poorly controlled Diabetes Mellitus.<sup>8</sup> In our study 46/57 = 80.7% of the diagnosed diabetics were uncontrolled. They were either on oral irregular hypoglycemics or alternate system of medicine or their diabetes was not controlled even after regular medications.

An increased susceptibility of patients with diabetes mellitus to develop tuberculosis could be due to neutrophil dysfunction & important cytokines production.<sup>9</sup> Interferon alpha producing capacity of WBC culture has been found to be reduced in patients of diabetes mellitus as well as tuberculosis patients.<sup>9</sup> Tsukaguchi *et al*<sup>10</sup> found a significant lowered production of IL-1 $\beta$  & TNF $\alpha$  by peripheral blood monocytes in patients with tuberculosis and co existing diabetes mellitus compared to patients with tuberculosis who do not suffer from diabetes mellitus. Production of IL-1 $\beta$  & TNF $\alpha$  was significantly lower in patients with poor glycemic control.<sup>10</sup> Increased susceptibility to tuberculosis is also due to thickened alveolar epithelium & pulmonary basal lamina, decrease pulmonary diffusion capacity, lung volume and elastic recoil in patients with diabetes mellitus.

Pathogenesis of these changes is currently thought to be due to non enzymatic glycosylation of tissue proteins inducing an alteration in connective tissue in diabetes mellitus.<sup>11</sup> This thickening in alveolar epithelium may decrease the bacillary growth because of the lower oxygen availability for the TB bacilli. But the alveolar thickening may not be that much to lead on to sufficient fall in oxygen levels that decrease the growth. Or as earlier stated, the locally higher glucose levels due to hyperglycemia may overpower this decreased oxygen content and become more significant to cause the bacillary proliferation. Further diabetic autonomic neuropathy also leads to abnormal basal airway tone due to alteration in vagal pathways and thus causing reduced bronchial reactivity and bronchodilation.<sup>11</sup>

The degree of hyperglycemia has been found to have a distinct influence on the microbicidal function of macrophages, with even brief exposures to blood sugar level of 200 mg% significantly depressing the respiratory burst of these cells.<sup>12,13</sup> This is borne out by the observation that in poorly controlled diabetics, with high levels of glycated haemoglobin, tuberculosis follows a more destructive course and is associated with higher mortality.

Pulmonary tuberculosis occurs predominantly in lung apices. It has been suggested that in patients with diabetes mellitus, tuberculosis occur predominantly in lower lobe with frequent cavitory lesions.<sup>14</sup> In other studies also, cavitory disease and multi-lobe involvement was found to be more common in patients with pulmonary tuberculosis and diabetes.<sup>15</sup>

However, in recent case control study, distribution of lesions including cavitory lesions was found to be similar in chest radiographs of tuberculosis patients with or without diabetes mellitus.<sup>16</sup> Our study showed that 68 patients had atypical presentations with either lower lobe involvement, multi lobe involvement, cavitations or shadows fanning out from the hilum. The atypical images of pulmonary tuberculosis in diabetic patients have been vaguely attributed to an immune abnormality and perfusion differences. It is known that diabetes mellitus causes a decrement in the activity of lymphocytes and a diminution in the number of monocytes and macrophages with abnormalities

in their chemotactic and phagocytic activities.<sup>10</sup> Moreover, diabetes also produces dysfunction of polymorphonuclear leukocytes, with a reduction in their bactericidal activity. Whilst more research is needed to clarify the role (if any) of leukocytes, the 'premature aging' of the lung induced by diabetes seems to be the main factor responsible for the development of the 'atypical' radiological pattern.

## CONCLUSION

The atypical radiological images like lower lobe involvement, fanning out from hilum or pneumonia like picture could mask the diagnosis of tuberculosis in diabetic patients, making the clinician think of diagnostic possibilities other than tuberculosis, with a consequent delay in the administration of proper treatment, causing far advanced or disseminated TB. Patients with TB and diabetes usually have uncontrolled diabetes. In patients of TB, diabetes may get enmasked because of the stress and infection and patients started on ATT with rifampicin containing regimens may, require increased doses of oral hypoglycemics. In a patient of diabetes having poor control and symptomatology suggestive of TB, TB should be suspected. Patients put on rifampicin containing regimens should have their oral hypoglycemic doses modified for proper and strict glycemic control. To achieve the target level of control, drugs rather than diet should be used. Also a high index of suspicion is required in reading the X-ray films, before making the diagnosis, especially in immunocompromised states like Diabetes mellitus. Proper control of diabetes is important as it can act as a double edged weapon leading to pulmonary TB and delay in diagnosis because of atypical presentations.

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