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Original Research Paper

Pulmonary Medicine

TO STUDY THE EFFECT OF MYCOBACTERIUM TUBERCULOSIS INFECTION AND ANTI TUBERCULOSIS TREATMENT ON SERUM MAGNESIUM LEVEL AT IRD, SMS MEDICAL COLLEGE, JAIPUR

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ABSTRACT

Background: Malnutrition and tuberculosis are both problems of considerable magnitude in most of the underdeveloped regions of the world. Magnesium ion concentration of blood is inversely proportional to the type and extent of the disease which could possibly be due to chronic malnutrition and the amount and destruction of lung tissue in cases of pulmonary tuberculosis. This study is to see the effect of mycobacterium tuberculosis infection and anti-tuberculosis treatment on serum magnesium level. **Material & Methods:** A hospital based longitudinal case control study done on all outdoor and indoor diagnosed patients of Pulmonary Tuberculosis (PTB), Multidrug-resistant Pulmonary Tuberculosis (MDRPTB) and healthy controls in IRD, Jaipur. 56 diagnosed cases of pulmonary tuberculosis before starting treatment (group PTB at initial) were followed after 2 months of treatment (group PTB at the end of intensive phage). 56 diagnosed case of multi drug resistant pulmonary tuberculosis (group MDRPTB). 56 age and sex matched healthy controls were taken and every candidate was examined for serum magnesium. **Results:** Our study showed that the maximum numbers of patients (54.76%) were in the age group of 31-50 years, male preponderance (57.14%). It was observed that Mg++ levels were significantly decreases in PTB and MDRPTB cases as compared to control group. The Mg++ levels were also found to be significantly lower in MDRPTB patients as compared to PTB patients (p=0.0047*). The mean value of serum magnesium level was significantly lower in malnourished patients (1.575±0.012 mg/dl) compare to normal BMI patients (1.585±0.011 mg/dl), (p-value<0.001*) and was statistically significant at initial in PTB group. The comparison of type of lesion & severity of disease with serum magnesium level was statistically significant at initial and at the end of intensive phase in PTB group. **Conclusion:** We concluded that decreased serum magnesium is a constant finding during pulmonary tuberculosis. In order to better understand the role of magnesium in pulmonary tuberculosis further clinical studies are required. Randomized controlled trials are warranted to generate higher levels of evidences to support our findings.

KEYWORDS : Pulmonary Tuberculosis, Serum Magnesium, PTB, MDRPTB, Malnutrition

INTRODUCTION:

Tuberculosis (TB) is an infectious disease caused by mycobacterium tuberculosis. Its morbidity and mortality are linked to socio-economic indices and lifestyle factors. The problem of tuberculosis is universal, with nearly a third of the world's population infected and nearly 1.6 million people dying annually from the disease of tuberculosis.[1]Tuberculosis is one of the most important public health problems in India. It is present since many centuries and most commonly affects people from low socio economic status. The Global TB Report 2021, the estimated incidence of all forms of TB in India for the year 2020 was 188 per 100,000 populations (129-257 per 100,000 populations). The estimated mortality rate among all forms of TB was 37 per 100,000 populations (34-40 per 100,000 populations) in 2020, as per the Global TB Report 2021. There has been a slight increase in the mortality rate due to all forms of TB between 2019 and 2020 by 11% in the country. In absolute numbers, the total number of estimated deaths from all forms of TB excluding HIV, for 2020 was 4.93 lakhs (4.53-5.36 lakhs) in the country, which was 13% higher that of the year 2019 estimate.[2]

The global TB epidemic like situation is further aggravated by HIV infection and emergence of drug-resistant tuberculosis.[3] A particularly dangerous form of drug-resistant Tuberculosis is Multidrug-Resistant Tuberculosis (MDR-TB), which is defined by WHO as the disease caused by TB bacilli resistant to at least isoniazid and rifampicin, the two most prescribed anti-TB drugs.[4] It is a serious threat to TB control programme and requires new guidelines for its management.[3] Malnutrition and tuberculosis are both problems of considerable magnitude in most of the underdeveloped regions of the world. It is important to consider, how these two problems tend to interact with each other. Malnutrition may predispose people to the development of clinical disease and tuberculosis can contribute to malnutrition.[5] Substantial experimental evidence suggests that malnutrition can lead to secondary immunodeficiency that increases the host's susceptibility to infection. Diagnosis of tuberculosis in National Tuberculosis Elimination Program (NTEP) is still based on sputum AFB microscopy and culture is considered as gold standard.[4] To improve the diagnosis of Tuberculosis (TB), more rapid diagnostic techniques have been investigated in recent years. Magnesium is one of the important minerals present in the human body as its role in enzymatic reactions and as a co-factor. Magnesium is the fourth most abundant intracellular cation present in the body. It may exist as protein bound, complexes or in free form. It is primarily found within the cell, where it acts as a counter ion for the energy-rich ATP and nucleic acids. It is a cofactor in more than 300 enzymatic reactions. Magnesium critically stabilizes enzymes, including many ATP generating reactions.[6] It is also key component in various reactions that require kinases and important factor in both cellular and humoral immune reactions.[7,8]

Magnesium ion concentration of blood is inversely proportional to the type and extent of the disease which could possibly be due to chronic malnutrition and the amount and destruction of lung tissue in cases of pulmonary tuberculosis. General debility in PTB patients can be suggested by hypomagnesaemia. It has been observed that Mg++ level was lower in PTB and MDR PTB compared to healthy controls

that can be explained by extent of damage and it can also be used to measure the response to treatment.[9] This study is to see the effect of mycobacterium tuberculosis infection and anti-tuberculosis treatment on serum magnesium level.

MATERIAL & METHODS:

A hospital based longitudinal case control study done on all outdoor and indoor diagnosed patients of Pulmonary Tuberculosis (PTB), Multidrug-resistant Pulmonary Tuberculosis (MDRPTB) and healthy controls in IRD, Jaipur.

Inclusion Criteria:

- Patients with having microbiologically confirmed Pulmonary Tuberculosis (PTB), Multidrug-resistant Pulmonary Tuberculosis (MDRPTB) and healthy controls.
- All pulmonary tuberculosis patients and healthy controls giving written informed consent.

Exclusion Criteria:

1. Sputum negative TB.
2. EPTB (Extra Pulmonary Tuberculosis)
3. Malabsorption syndrome
4. Renal diseases without azotemia.
5. Post-parathyroidectomy.
6. Prolonged use of diuretics.
7. Chronic alcoholism.
8. Ischaemic heart diseases.
9. Epilepsy

Methodology:

A detailed data regarding demographic characteristics, socioeconomic status, Clinical history regarding total duration of illness and Previous history of anti tuberculosis therapy-duration, type of drug- govt (NTEP) regimen /private regimen, family history of anti-tuberculosis therapy and any contact with tuberculosis patients were obtained.

Clinical Examination -

A thorough examination of the patient was done. All vitals were recorded. Patient's height weight and body mass index was recorded. Those patients whose BMI was less than 18.5 were labeled as malnourished. Both general and systemic examination was done. Patients who were seen as an outpatient were examined in the first visit and regularly followed up. Patient who needed admission were admitted and followed up.

PROCEDURE:

All the patients who were microscopically confirmed smear positive , approximately of 2ml each into two clean falcon tubes and these collected samples were immediately transported to the state accredited intermediate reference laboratory for testing. In this laboratory the samples were subjected to cartridge based nucleic acid amplification test (CBNAAT) followed by line probe assay (LPA) of first/ second line anti tuberculosis drugs and/or drug susceptibility testing (DST).

Patients Divided In Three Groups:

1. 56 age and sex matched healthy control after excluding inflammatory diseases (Control group).
2. 56 patients of newly diagnosed pulmonary TB patients twice, first before starting treatment and at the end of intensive phase of treatment that is after 2 months of treatment.
3. In 56 patients of newly diagnosed MDRPTB patients before starting treatment

Methods of measurements:

All patients and healthy control were subjected to detailed history and clinical examination. The blood sample in plain evacuated tube was allowed to clot at room temperature. It was then centrifuged at 3000 rpm for 10 minutes to separate serum; samples were stored at -20^0 C for further batch analysis for serum magnesium level. Tests were carried out in fully automated clinical chemistry analyzer, Beckman Coulter (SYNCHRON CX9) using standard reagents/kits. For serum magnesium (mg/dl) analysis xylidyl blue method was used.

Statistical Evaluation:

The data obtained were analyzed by using statistical tests ANOVA, independent t-test and paired t-test for comparison between groups and p value was calculated, p value < 0.05 was taken as a significant using Statistical Package of Social Sciences (SPSS) version 22.0.

RESULTS:

Our study showed that the maximum numbers of patients (54.76%) were in the age group of 31-50 years. Male preponderance (57.14%) as compare to female (table 1) in present study.

Table1: Demographic Variables In Between Groups

Demographic variables	Control (N=56)	PTB group (N=56)	MDR PTB Group (N=56)
Age (yrs)			
10-20	0	6	5
21-30	7	7	16
31-40	27	9	18
41-50	16	15	7
>50	6	19	10
Mean±SD	39.76±7.65	44.46±10.23	37.0±8.49
Gender			
Male	34	34	28
Female	22	22	28

In our study we estimated serum magnesium for all the subjects and results is shown in table-2. We applied statistical test ANOVA between all the groups and we found difference in mean of magnesium in all the groups to be statistically significant with p value < 0.001*. It was observed that Mg++ levels were significantly decreases in PTB and MDRPTB cases as compared to control group. The Mg++ levels were also found to be significantly lower in MDRPTB patients as compared to PTB patients (p=0.0047*). Independent t-test was applied to compare the difference in mean of magnesium between the control group and the study groups (PTB at initial, PTB at end stage of intensive phage and MDRPTB), which was found to be statistically significant (p<0.001*). Paired t-test was used to analyze treatment response in PTB patients the difference in mean of magnesium before (PTB-1) and after (PTB-2) starting treatment was observed to be statistically significant (p=0.001). After 2 months of anti tuberculosis treatment (ATT) magnesium levels were found to increase significantly, but were still lower as compared to the control group (table 2).

Table 2: Serum Magnesium Level In Control And Study Group

Groups	No.	Serum Magnesium level (mg/dl) Mean±SD	P value compared to control	P value compared to PTB at initial
Control	56	1.80±0.26	-	-
PTB group (at initial)	56	1.58±0.24	<0.001**	-
PTB group (at end of intensive phase)	56	1.75±0.33	<0.001**	<0.001**
MDR PTB group	56	1.53±0.23	<0.001**	0.0047*

Our study showed that the mean value of serum magnesium level was significantly lower in malnourished patients (1.575±0.012 mg/dL) than the normal BMI patients (1.585±.011 mg/dL), (p-value<0.001*) and was statistically significant at initial in PTB group. The comparison of BMI (Kg/m^2) and serum magnesium level was statistically significant at initial and at the end of intensive phase in PTB

group (table 3).

Table 3: Correlation Between Serum Magnesium Level And BMI In PTB Group At Initial, At The End Of Intensive Phase And MDRPTB Group

BMI (Kg/M^2)	No. Of cases	PTB group at initial	PTB group at the end of intensive phase	P-value	MDRPTB group	P-value
Malnourished	33	1.575±0.012	1.7512±0.013	<0.001*	1.537±0.09	<0.001*
Normal	23	1.585±.011	1.7521±0.07	<0.001*	1.546±0.010	<0.001*

The present study showed that the mean serum magnesium level was significantly lower in cavitary type (1.578±0.0524 mg/dL) than the non- cavitary type (1.585±.0631 mg/dL), (p-value<0.001*) and was statistically significant at initial in PTB group. In the end of intensive phage, the mean value of serum magnesium level was significantly lower in cavitary type (1.7519±0.0730 mg/dL) than the non-cavitary type (1.7521±0.0546 mg/dL), (p-value>0.05) and was statistical non- significant. The comparison of type of lesion and serum magnesium level was statistically significant at initial and at the end of intensive phage in PTB group (table 4).

Table 4: Correlation Between Serum Magnesium Level And Different Radiological Lesion In PTB Group At Initial, At The End Of Intensive Phase And MDRPTB Group

Type of lesion	PTB group at initial	PTB group at the end of intensive phase	P-value	MDRPTB group	P-value
Cavitary	1.578±0.0524	1.7519±0.0730	<0.001*	1.537±0.065	<0.001*
Non-cavitary	1.585±.0631	1.7521±0.0546	<0.001*	1.549±0.058	<0.001*

In far advanced disease (1.542±0.0237 mg/dL) the serum magnesium levels were lower than in moderately advanced (1.571±0.0211 mg/dL) and minimal Disease (1.585±0.0246 mg/dL) (p- value<0.001*) at initial in PTB group. In PTB group at the end of intensive phase the far advanced disease (1.7497±0.0312 mg/dL) the serum magnesium levels were lower than in moderately advanced (1.7508±0.0238 mg/dL) and minimal Disease (1.7521±0.0245 mg/dL) (p-value<0.001*). The comparison of severity of disease and serum magnesium level was statistically significant at initial and at the end of intensive phase in PTB group (table 5).

Table 5: Correlation Between Serum Magnesium Level And Severity Of Pulmonary Tuberculosis In PTB Group At Initial, At The End Of Intensive Phase And MDRPTB Group

Severity of Pulmonary Tuberculosis	PTB group at initial	PTB group at the end of intensive phase	P-value	MDRPTB group	P-value
Minimal	1.585±0.0246	1.7521±0.0245	<0.001*	1.549±0.0213	<0.001*
Moderately advance disease	1.571±0.0211	1.7508±0.0238	<0.001*	1.537±0.0218	<0.001*
Far advance disease	1.542±0.0237	1.7497±0.0312	<0.001*	1.524±0.0228	<0.001*

DISCUSSION:

Tuberculosis patients in India get treatment with DOTS regimen not only through National Tuberculosis Elimination Program (NTEP), but also receive treatment from private medical practitioners, therefore involvement and coordination of both groups of medical practitioners is required for effective management of Tuberculosis. Irregular, incomplete and inadequate treatment is the most common means of acquiring drug resistant organism.

Our study showed that the maximum numbers of patients (54.76%) were in the age group of 31-50 years. This may be due to their more social contacts, social activities and out-door work and also this age group may seek medical facility earlier. The comparison of mean value of age was statistical non-significant in between groups. Also in children diagnosis is difficult for reasons such as lack of sputum production and early use of antibiotics. Male preponderance (57.14%) as compare to female in our study maybe due to vulnerability of their social contacts, exposure to challenging and hazardous working environment and men seeking early medical care. In females due to, social stigma, myths about tuberculosis, non-accessibility of services may be the reason for this discrepancy. Our study supported with Yuthika Agrawal et al.[10] found median age of the participants was 45 (15-75) years & most participants (67%) were males. Another study done by Jemil S Makadia et al[11] revealed that maximum numbers of patients (70%) were in the age group of 20-40 years and it was more common in male (56.66%) than female (43.33%).

Magnesium ion concentration of blood is inversely proportional to the type (drug sensitive and drug resistant PTB) and extent of the disease (minimal, moderately advanced and far advanced disease) which could possibly be due to chronic malnutrition and the amount and destruction of lung tissue in cases of pulmonary tuberculosis.[12] General debility in PTB patients can be suggested by hypomagnesaemia. It has been observed that Mg++ level was lower in MDRPTB compared to PTB that can be explained by extent of damage and it can also be used to measure the response to treatment.

Ali Raza Memon et al (2014)[13] found that Serum magnesium levels in controls and in patients determined to be 1.69±0.160 mg/mL and 1.21±0.083mg/mL respectively. Serum magnesium was found statistically decreases in patients as compared with the controls.

Jemil S Makadia, Anju Jain (2016)[11] found that serum magnesium level in pulmonary tuberculosis (PTB) was 1.61±0.24 mg/ml and in MDR-PTB 1.47± 0.23 mg/ml were significantly lower compared to control (2.07±0.3 mg/ml) (p value <0.001). In follow up cases of PTB after 2 months of treatment, though levels showed an increase compared to pre-treatment value (p value <0.001), still the levels were significantly lower than control group (p value <0.001). The magnesium levels were also found to be significantly lower in MDRPTB patients as compared to PTB patients (p=0.004), which was compatible with our results.

The comparison of BMI (Kg/m^2) and serum magnesium level was statistically significant at initial and at the end of intensive phase in PTB group in our study. Jemil S Makadia, Anju Jain (2016)[11] concluded that magnesium ion concentration of blood is inversely proportional to the type and extent of the disease which could possibly be due to chronic malnutrition and the amount and destruction of lung tissue in cases of pulmonary tuberculosis and it can also be used to measure the response to treatment.

A study done by Dr Irfan et al (2017)[10] showed serum magnesium level was significantly lower in cavitary type (1.571±0.052 mg/dL) than the non-cavitary type (1.675±0.026 mg/dL). Which was compatible with our result observed that the comparison of type of lesion and serum magnesium level was statistically significant at initial and at the end of intensive phase in PTB group.

The comparison of severity of disease and serum magnesium level was statistically significant at initial and at the end of intensive phase in PTB group in our study. A similar study done by Dr Irfan et al (2017)[10] observed that in far advanced disease (1.537±0.054) the serum magnesium levels were lower than in moderately advanced (1.606±0.023) and minimal disease (1.675±0.026). Jain et al (1976)[12] also found that serum Mg++ level in minimal, moderately and far advanced tuberculosis were 1.90, 1.78 ± 0.177 and 1.608 ± 0.242 respectively. In follow up cases of PTB after 2 months of ATT, though serum Mg++ levels showed an increase compared to pre-treatment value (p value 0.001), still the levels were significantly lower than control group (p value <0.001).

Hypomagnesaemia in malnutrition has been observed in pulmonary tuberculosis patients. Enhancement of magnesium deficiency through magnesium supplement may be effective in pulmonary tuberculosis patients, and achieving better therapeutic results, but further investigation is needed.

CONCLUSION:

Magnesium ion concentration of blood is inversely proportional to the type (drug sensitive and drug resistant PTB) and extent of the disease (minimal, moderately advanced and far advanced disease) which could possibly be due to chronic malnutrition and the amount and destruction of lung tissue in cases of pulmonary tuberculosis and it can also be used to measure the response to treatment. We concluded that decreased serum magnesium is a constant finding during pulmonary tuberculosis. In order to better understand the role of magnesium in pulmonary tuberculosis further clinical studies are required. Randomized controlled trials are warranted to generate higher levels of evidences to support our findings.

Limitation:

Our study had some limitations as well. First, small sample size is an evident limitation of this study. Second, mycobacteria cultures should also have been performed after giving ATT for two months, as non-viable mycobacteria can give false positive results. Thirdly, bias is possible due to non-adherence to ATT as it is an important factor for sputum conversion and cure of TB.

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