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Research Article

STUDY OF CYTOKINES AND OXIDATIVE STRESS PARAMETERS IN PULMONARY TUBERCULOSIS

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A B S T R A C T

Background: The protective immunity to Mycobacterium tuberculosis (Mtb) is mediated by cytokines produced by macrophages and T cells. Oxidative stress and cytokine markers were studied to estimate the risk factors and its consequence as the diseaseprogresses.
Methods and Materials: Case – Control study comprised of 50 Controls, 50 newly diagnosed Tuberculosis (TB) patients (Category I) and 50 TB patients showing multidrug-resistance (MDR). Recruited subjects were of both genders in 18-60 years of age group. Serum samples were analysed by Chemiluminescence and Spectrophotometry. Statistical evaluation was done by Pearson correlationusing Minitab 17 software.
Results: Serum levels of Cytokines Interleukin-1, Interleukin-2, Interleukin-6 and α-Tumor Necrosis Factor, Malonyldialdehyde, Nitric Oxide and Protein carbonyl were significantly increased in Category I and MDR TB patients as compared to normal healthy controls.
Conclusion: This study concludes that in tuberculosis, the serum levels of cytokines and stress parameters increase as the disease progresses from initial stage of infection to drug resistance.

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INTRODUCTION

Mycobacterium tuberculosis (Mtb), the etiologic agent of tuberculosis, is responsible for more human deaths each year than any other single pathogen (Matthew J. Fenton *et al*. 1997). The central dogma of protective immunity to Mtb is the interplay between Mtb-infected macrophages and T cells, which is mediated by numerous cytokines produced by both cell types *(*Chang Ho Kim *et al*. 2015). Adaptive immunity is triggered when the bacterial infection eludes the innate defence mechanisms (Torrado E. *et al*. 2013). Evolution of the infection depends on bacterial virulence factors, nutritional state, host genetic condition and immune response (Alfred E. Fox).

M. tuberculosis (Mtb) survives a hostile environment within the host that is shaped in part by oxidative stress (Subhalaxmi Nambi *et al*. 2015). TB occurs because of dysregulation of the immune system and/or poor immune response against the infection. Innate immune response critically acts against Mtb infection. Mtb is recognized intracellular bacteria that replicates and grow within macrophages. Mtb can stimulate activated macrophages to produce reactive oxygen species (ROS), which is an important part of host defense against mycobacterium (Vishal Wagh *et al*. 2016). Oxidative stress, caused by an imbalance in reactive oxygen species (ROS) produced during normal cell metabolism and/or efficiency of scavenger antioxidant defense (Maureen Jepkorir Chesereket *et al*. 2015).

The Interleukin-1 family (IL1 family) is a group of 11 potent proinflammatory cytokines, playing a central role in the regulation of immune and inflammatory responses to infections. Interleukin-1 (IL-1) is produced at the site of infection during tuberculosis (TB) and is involved in the regulation of Th1/Th2 immune responses to infection with intracellular pathogens (Nicole P. Juffermans *et al*. 2000). Interleukin-2 (IL-2), a cytokine produced by activated T lymphocytes, has a central role in the activation and expansion of T cells. It is part of the body's natural response to microbial infection, and in discriminating between foreign and self materials. Patients with TB frequently have deficient IL2–induced cell proliferation and decreased IL2 receptor generation (Toossi Z *et al*. 1986).

Alpha tumor necrosis factor (α-TNF) is another major cytokine for an immune response against Mtb. It stimulates the phagocyte capacity of macrophages synergising with IFN-γ. Moreover, α-TNF is also responsible for the granuloma formation, and is involved in both immune and immune-modulatory responses (RenataZrinskiTopić, 2012). *In*

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particular, CD4+ T cells play a major role by producing IFN-γ, which synergizes with α-TNF and potentiates macrophages that are capable of restricting the growth of Mtb. Thus, the evaluation of cytokine expression elicited by the cellular responses to Mtb-specific antigen has been exploited as one way to detect TB infection *(*Chang Ho Kim *et al*. 2015). α-TNF therefore plays a critical role in host response to mycobacterial infection, via its role in macrophage activation, cell recruitment, granuloma formation, and maintenance (Sarah K. Brode *et al*. 2012). Nitric oxide (NO) is an important molecule to study the oxidative stress markers in the bacterial infections as it serves as a pro-oxidant molecule. NO is also an important mediator of immune homeostasis (Vishal Wagh *et al*. 2016). Malonyldialdehyde (MDA) is a decomposition product of oxidized polyunsaturated fattyacids. This three-carbon dialdehyde has beenproposed to arise from fatty acid hydroperoxides via several mechanisms. The most frequent precursors of MDA are five membered hydroperoxyepidioxides (endoperoxides) and 1,3-dihydroperoxides. Most lipid hydroperoxides are unstable and undergo decomposition to secondary lipid peroxidation products such as MDA (Rajinderjeet Singh Ahi *et al*. 2012).

A very important marker of oxidative stress is protein carbonylation, measured through estimating protein carbonyl groups content in serum. Measuring protein carbonyl content is advantageous over other biomarkers of oxidative stress due to their early formation and detectable stability arising from protein side chains (Pro, Arg, Lys, and Thr). Proteincarbonylation is a type of protein oxidation that can be promoted by reactive oxygen species. It usually refers to a processthat forms reactive ketones or aldehydes that can be reactedby 2,4-dinitrophenylhydrazine (DNPH) to form hydrazones.Oxidative modification of proteins is known to affect protein function. The protein carbonyl (PC) group are formed by either direct oxidation of certain amino acid residues, particularly lysine, arginine, threonine, proline, and histidine or secondarily reaction with product of lipid peroxidation or glycoxidation reaction with lysine group (Vaishali Kolgiri *et al*. 2017).

The aim of this study was to evaluate the serum levels of cytokines IL1, IL2, IL-6, α-TNF, MDA, NO and Protein carbonyl between controls and newly diagnosed TB patients and those showing multi-drug resistance in response to anti-TB treatment. An effect of treatment on these oxidative stress markers was also studied to estimate whether the variables are risk factors for tuberculosis or a consequence and progression of the disease.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

The Case–Control study comprised of 50 normal healthy human volunteers (Control), 50 newly diagnosed TB patients (CAT I) and 50 TB patients treated with dots showing multidrug-resistance (MDR). Recruited subjects were of both genders in age group of 18- 60 years and from different socioeconomic status. Patients admitted and those visiting Out Patient Department at Sir J.J. group of Hospitals, Mumbai were included in study. Subjects not willing to participate in the study and HIV positive were excluded.

METHOD

Blood serum samples were collected, stored at -80°C and analysed for IL-1, IL-2, IL-6 and α-TNF by Chemiluminescent Immulite 1000, Siemens Medical Solutions Diagnostics, a solid- Phase, enzyme-labelled, chemiluminescent sequential immunometric assay. Spectrophotometer was used to estimate MDA by Buege and Aust method, NO by Najwa K., Cortas and Nabil W. Wakid method and Protein carbonyl by Levine method. Ethical Clearance approval was taken from the institutional ethics committee of Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai and informed consents along with details of patients were taken prior to the study.

Evaluation

Statistical evaluation was analysed by Pearson correlation nusing Minitab 17 software. Statistical significance was accepted at $P<0.05$ and data were interpreted using 95% confidence interval.

RESULTS

Table 1 Age and Sex Wise Distribution in Control and Pulmonary Tuberculosis

Group (n=50)	Age(Mean ± SD)	Sex	
		Male	Female
Control	37.06 ± 10.01	25	25
Pulmonary Tuberculosis			
Category I	32.3 ± 9.34	25	25
Multi drug resistant (MDR)	33.66 ± 11.05	25	25

Table 2 Levels of Malonyldialdehyde (MDA), Nitric oxide (NO), Protein carbonyl (PC), Cytokines Interleukin 1 (IL-1), Interleukin 2(IL-2), Interleukin 6 (IL-6) and Alpha tumor necrosis factor (α-TNF) in Control and Pulmonary Tuberculosis.

Group (n=50)	MDA (nmol/ml) Mean ± SD	NO (µmol/L) Mean ± SD	PC (nmol) Mean ± SD	IL1 Levels (pg/mL) Mean ± SD	IL2 Levels (U/mL) Mean ± SD	IL-6 (pg/mL) Mean ± SD	α–TNFLevels (pg/mL) Mean ± SD
Control	2.47 ± 0.131	35.69 ± 0.68	4.37 ± 0.14	3.2 ± 0.93	422.16 ± 130.15	3.4 ± 119.92	15.88 ± 4.26
Category I	5.42 ± 0.38	58.63 ± 3.57	6.72 ± 0.19	16.23 ± 3.19	825.69 ± 157.49	8.2 ± 14.08	21.61 ± 5.43
MDR	8.78 ± 0.66	70.81 ± 2.71	7.09 ± 0.21	68.398 ± 22.13	1251.28 ± 269.46	74.61 ± 109.34	109.09 ± 137.77

Table 3 A Correlations of MDA with MDA, NO, PC, IL-1, IL-2, IL-6 and α–TNF in Control and Pulmonary Tuberculosis groups

Sr. No.	r -value	p-value	r -value	p-value	r -value	p-value
	Control/Category I		Control/MDR		Category I/MDR	
1	**MDA / MDA**		**MDA / MDA**		**MDA / MDA**	
	0.026	0.859	0.028	0.849	0.032	0.825
2	**MDA / NO**		**MDA / NO**		**MDA /NO**	
	-0.119	0.412	0.296	0.037	0.296	0.037
3	**MDA / PC**		**MDA / PC**		**MDA / PC**	
	0.014	0.922	-0.029	0.841	-0.020	0.891
4	**MDA / IL-1**		**MDA / IL-1**		**MDA / IL-1**	
	0.292	0.040	-0.008	0.955	-0.304	0.032
5	**MDA / IL-2**		**MDA / IL-2**		**MDA / IL-2**	
	0.149	0.302	0.121	0.404	-0.284	0.045
6	**MDA / IL-6**		**MDA / IL-6**		**MDA / IL-6**	
	-0.018	0.903	-0.020	0.891	0.037	0.800
7	**MDA / α–TNF**		**MDA / α–TNF**		**MDA / α–TNF**	
	-0.211	0.142	-0.022	0.881	-0.160	0.267

Table 3 B Correlations of NO with MDA, NO, PC, IL-1, IL-2, IL-6 andα–TNF in Control and Pulmonary Tuberculosis groups

Sr. No.	r -value	p-Value	r –value	p-Value	r –value	p-Value
	Control/Category I		Control/MDR		Category I/MDR	
1	NO / MDA		NO / MDA		NO / MDA	
	0.353	0.012	-0.315	0.026	0.162	0.261
2	NO / NO		NO / NO		NO / NO	
	-0.086	0.553	0.066	0.650	-0.154	0.286
3	NO / PC		NO / PC		NO / PC	
	0.096	0.509	0.090	0.532	0.029	0.839
4	NO / IL-1		NO / IL-1		NO / IL-1	
	0.105	0.467	-0.382	0.006	0.155	0.281
5	NO / IL-2		NO / IL-2		NO / IL-2	
	-0.043	0.765	0.041	0.775	-0.045	0.756
6	NO / IL-6		NO / IL-6		NO / IL-6	
	-0.118	0.414	0.101	0.486	-0.149	0.301
7	NO / α–TNF		NO / α–TNF		NO / α–TNF	
	0.342	0.015	-0.427	0.002	0.052	0.720

Table 3C Correlations of PC with MDA, NO, PC, IL-1, IL-2, IL-6 andα–TNF in Control and Pulmonary Tuberculosis groups

Sr. No.	r -value	p-Value	r -value	p-Value	r -value	p-Value
	Control / Category I		Control / MDR		Category I / MDR	
1	PC / MDA		PC / MDA		PC / MDA	
	-0.104	0.472	0.041	0.777	0.059	0.682
2	PC / NO		PC / NO		PC / NO	
	0.472	0.001	-0.166	0.250	-0.023	0.872
3	PC / CP		PC / CP		PC / CP	
	-0.079	0.585	0.273	0.055	-0.034	0.815
4	PC / IL-1		PC / IL-1		PC / IL-1	
	-0.104	0.471	0.257	0.071	-0.129	0.372
5	PC / IL-2		PC / IL-2		PC / IL-2	
	-0.301	0.034	-0.026	0.860	0.059	0.684
6	PC / IL-6		PC / IL-6		PC / IL-6	
	0.143	0.320	0.260	0.068	-0.562	0.000
7	PC / α–TNF		PC / α–TNF		PC / α–TNF	
	-0.147	0.309	0.090	0.532	0.021	0.882

Table 3D Correlations of IL-1 with MDA, NO, PC, IL-1, IL-2, IL-6 andα–TNF in Control and Pulmonary Tuberculosis groups

Sr. No.	r -value	p-Value	r –value	p-Value	r -value	p-Value
	Control / Category I		Control / MDR		Category I / MDR	
1	IL-1 / MDA		IL-1 / MDA		IL-1 / MDA	
	0.053	0.715	0.289	0.042	0.181	0.209
2	IL-1 / NO		IL-1 / NO		IL-1 / NO	
	0.141	0.330	0.077	0.594	0.128	0.377
3	IL-1 / PC		IL-1 / PC		IL-1 / PC	
	-0.099	0.494	0.028	0.849	0.222	0.122
4	IL-1 / IL-1		IL-1/ IL-1		IL-1 / IL-1	
	0.011	0.941	0.055	0.704	-0.179	0.215
5	IL-1 / IL-2		IL-1 / IL-2		IL-1 / IL-2	
	-0.010	0.944	-0.316	0.025	-0.192	0.182
6	IL-1 / IL-6		IL-1 / IL-6		IL-1 / IL-6	
	0.084	0.563	0.108	0.454	0.181	0.208
7	IL-1 / α–TNF		IL-1 / α–TNF		IL-1 / α–TNF	
	-0.208	0.147	-0.060	0.679	-0.180	0.211

Table 3E Correlations of IL-2 with MDA, NO, PC, IL-1, IL-2, IL-6 andα–TNF in Control and Pulmonary Tuberculosis groups

Sr. No.	r -value	p-value	r -value	p-value	r -value	p-value
	Control / Category I		Control / MDR		Category I / MDR	
1	IL-2 / MDA		IL-2 / MDA		IL-2 / MDA	
	0.016	0.914	-0.014	0.924	0.168	0.245
2	IL-2/ NO		IL-2 / NO		IL-2 / NO	
	0.046	0.754	0.309	0.029	-0.099	0.495
3	IL-2 / PC		IL-2 / PC		IL-2 / PC	
	0.102	0.482	0.061	0.673	0.022	0.877
4	IL-2 / IL-1		IL-2 / IL-1		IL-2 / IL-1	
	0.051	0.724	0.203	0.157	0.039	0.791
5	IL-2 / IL-2		IL-2 / IL-2		IL-2 / IL-2	
	-0.115	0.426	-0.055	0.705	0.209	0.146
6	IL-2 / IL-6		IL-2 / IL-6		IL-2 / IL-6	
	0.080	0.581	-0.090	0.532	-0.390	0.005
7	IL-2 / α–TNF		IL-2 / α–TNF		IL-2 / α–TNF	
	-0.269	0.058	0.055	0.702	0.164	0.255

Table 3F Correlations of IL-6 with MDA, NO, PC, IL-1, IL-2, IL-6 andα–TNF in Control and Pulmonary Tuberculosis groups

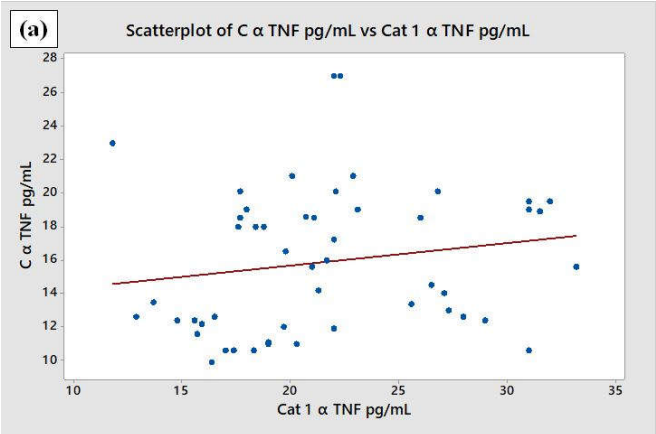
Sr. No.	r -value	p-Value	r -value	p-Value	r -value	p-Value
	Control / Category I		Control / MDR		Category I / MDR	
1	IL-6 / MDA		IL-6 / MDA		IL-6 / MDA	
	0.174	0.228	-0.118	0.413	-0.048	0.739
2	IL-6 / NO		IL-6 / NO		IL-6 / NO	
	0.265	0.063	-0.049	0.735	0.014	0.923
3	IL-6 / PC		IL-6 / PC		IL-6 / PC	
	0.070	0.628	0.037	0.797	0.369	0.008
4	IL-6 / IL-1		IL-6 / IL-1		IL-6 / IL-1	
	-0.300	0.034	0.231	0.107	-0.004	0.975
5	IL-6 / IL-2		IL-6 / IL-2		IL-6 / IL-2	
	-0.112	0.440	-0.176	0.220	0.144	0.319
6	IL-6 / IL-6		IL-6 / IL-6		IL-6 / IL-6	
	-0.053	0.714	-0.060	0.678	-0.126	0.383
7	IL-6 / α–TNF		IL-6 / α–TNF		IL-6 / α–TNF	
	0.002	0.990	0.166	0.250	-0.110	0.448

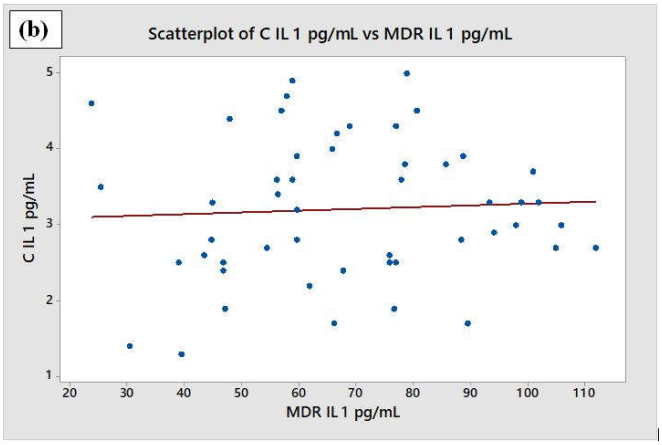
Table 3G Correlations of α–TNF with MDA, NO, PC, IL-1, IL-2, IL-6 and α–TNF in Control and Pulmonary Tuberculosis groups

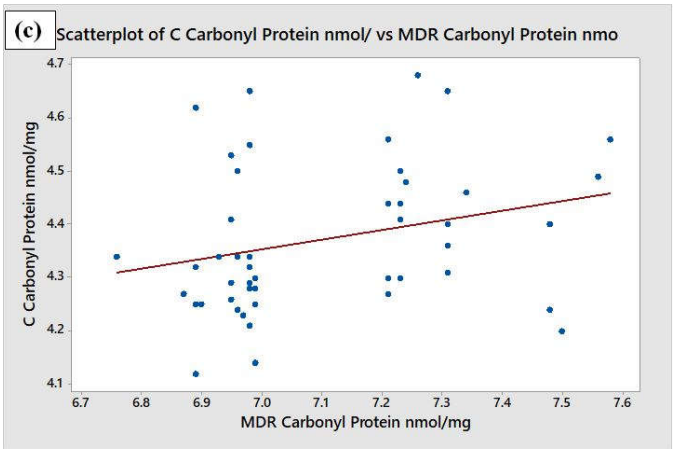
Sr. No.	r -value	p-Value	r -value	p-Value	r –value	p-Value
	Control / Category I		Control / MDR		Category I / MDR	
1	α–TNF / MDA		α–TNF / MDA		α–TNF / MDA	
	-0.014	0.925	0.010	0.947	-0.158	0.272
2	α–TNF / NO		α–TNF / NO		α–TNF / NO	
	0.041	0.775	-0.129	0.372	-0.280	0.049
3	α–TNF / PC		α–TNF / PC		α–TNF / PC	
	0.165	0.254	0.179	0.212	0.239	0.094
4	α–TNF / IL-1		α–TNF / IL-1		α–TNF / IL-1	
	-0.040	0.781	0.012	0.934	-0.079	0.587
5	α–TNF / IL-2		α–TNF / IL-2		α–TNF / IL-2	
	0.121	0.404	0.047	0.745	0.146	0.311
6	α–TNF / IL-6		α–TNF / IL-6		α–TNF / IL-6	
	0.207	0.149	-0.361	0.010	-0.274	0.055
7	α–TNF / α–TNF		α–TNF / α–TNF		α–TNF / α–TNF	
	0.171	0.235	-0.097	0.505	-0.182	0.207

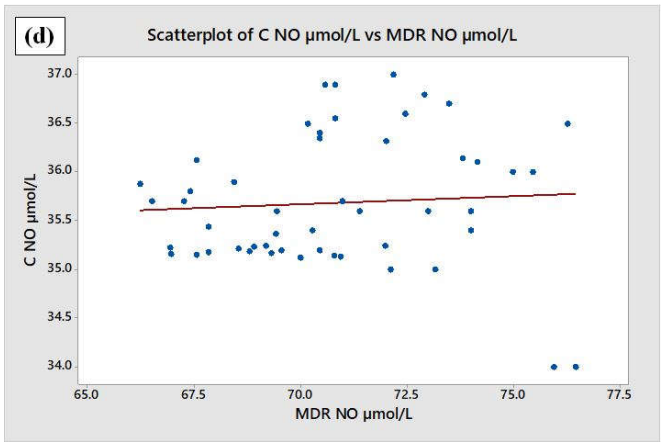
Table 4 Socioeconomic Status Distributions in Pulmonary Tuberculosis

Socioeconomic class	I	II	III	IV	V
No. of cases (**CAT I**)	0	1	21	14	14
No. of cases (MDR)	0	10	10	14	16









Graphs Regression graphs of correlations**(a)** C α-TNF vs Cat 1 α-TNF **(b)** C IL1 vs MDR IL1 **(c)** C Protein Carbonyl vs MDR Protein Carbonyl **(d)**C NO vs MDR NO

DISCUSSION

Oxidative stress is a situation that occurs in biological systems when there is a disruption of the balance between antioxidants and freeradicals. Oxidative stress in tuberculosis (TB) may be due to tissue inflammation, poor dietary intake of micronutrients, and release of free radicals from macrophages and side effects of anti-TB drugs (Brown Holy *et al*. 2018).**Table 4** displays the socioeconomic distributions in the study groups indicating the involvement of maximum TB patients having low socioeconomic status. Also, the age-sex wise distribution of patients recruited in the study is shown in **Table 1**.Despite the fact that effective drugs have been available for years, millions of cases of the disease still abound. The emerging problem of the drug-resistant strains of the mycobacterium tuberculosis complex has also contributed to the difficulty of TB eradication (Valeria Sargentini *et al*. 2009).

The assessment of oxidative stress markers is not in the regimen in the management of TB patients. This has affected the outcome of TB patient's thereby increasing mortality rate. Hence, measurement of oxidative stress markers may be an index of monitoring response to treatment in tuberculosis management (Brown Holy *et al*. 2018).

In the present study levels of MDA, NO, Protein carbonyl, IL-1, IL-2, IL-6 and α–TNF were found to be significantly increased in serum of TB infected individuals compared to healthy controls. Also, the increased values of oxidative parameters were observed as the disease progresses to drug resistance as shown in Table 2. Many studies have shown similar results of raised oxidative stress levels in Tuberculosis patients 9Vishal Wagh *et al*. 2016, Brown Holy *et al*. 2018, Rashmi Kulkarni *et al*. 20130. Kulkarni R *et al* conducted a study of serum malondialdehyde (MDA) and TNF-α in TB patients. TNF α and MDA levels in serum were significantly increased in pulmonary TB patients as compared to those of controls (Rashmi Kulkarni *et al*. 2013).In the study by Wagh V *et al*.2016, NO levels were significantly raised in TB population as compared to healthy control ($p<0.0001$)(Vishal Wagh *et al*. 2016). The serum levels of cytokines and stress markers in MDR group TB patients was significantly high than those in Category I TB patients which is shown in Table 2 and 3A-3G. On statistical evaluation, the correlation between MDA, NO, Protein carbonyl, IL-1, IL-2, IL-6 and α–TNF in Control, Category I and MDR groups showed positive correlation. The insignificant correlation indicates a rise in serum levels of all the stress markers in TB patients along with the progression of the disease.

Since oxidative environment is crucial for survival of the Mtb, it appears that Mtb alters the host physiology biasing towards pro-oxidative environment. Such an adaptation of the host by the bacteria would be beneficial for the survival and proliferation of the pathogen. Since high oxidative stress is also favourable for the other pathogen like HIV, it is possible that modulation of the host oxidative stress machinery might further aid in developing co-infections. It will be of interest to determine the levels of oxidative stress molecules in patients with and without co-infection to understand the role of oxidative stress in TB pathophysiology (Vishal Wagh *et al*. 2016).

CONCLUSION

This study concludes that in tuberculosis, the serum levels of cytokines and stress parameters increase as the disease progresses from initial stage of infection to drug resistance. Considering that the antigenic stimulus for cytokine production is the infection by Mtb and taking into account the study data, we can assume that the production of cytokines is directly proportional to the bacterial load. Furthermore, the rise in serum cytokines may be related to the progression of the infection process.

We propose that sequential measurements of these mediators in serum may be useful in the monitoring of anti-tuberculosis therapy; not replacing clinical parameters of disease activity in TB, such as symptoms, chest X-rays and culture and smear results, but used in addition to these conventional parameters for treatment and prognosis of TB.

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