Adrenocortical Reserve in Patients with Active Tuberculosis

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Abstract

Context: In recent years several studies have documented decreased adrenal cortical reserve in patients with active tuberculosis. This reduced adrenal reserve could be an important factor in causing mortality and morbidity in these patients.
Objective: To study the adrenal cortical reserve and its relationship with disease duration and severity in patients with active tuberculosis.
Design, Sethng and participants: Forty patients with confirmed active tuberculosis (28 pulmonary and 12 extra-pulmonary) without clinical evidence of Addison's disease and 10 healthy, age and sex-matched subjects (controls) participated in this study. The study was conducted at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir.
Interventions: Adrenocorticotropic hormone stimulation test performed in both groups.
Main Outcome Measures: Basal serum cortisol level and parameters of stimulated cortisol response (maximum increase of cortisol over basal, peak rise of cortisol and area under response curve).
Results: The mean basal cortisol levels were comparable between the two groups (P=0.792). The parameters of stimulated cortisol response including maximum increase of cortisol over basal, the peak rise of cortisol and area under response curves were significantly lower in patients as compared to healthy controls (P<0.001, 0.002 and 0.049 respectively). However, these parameters were comparable between patients with active pulmonary and extra-pulmonary tuberculosis. Overall 14 (35%) patients exhibited sub-optimal cortisol response (3 negligible and 11 inadequate) to ACTH stimulation. ACTH stimulation revealed significant cortisol rise in patients with active tuberculosis at 4 and 8 hours only, whereas in healthy controls, the cortisol rise was more prolonged and continued up to 24 hours. The adrenocortical reserve was inversely related to the radiological severity of pulmonary tuberculosis (r, -0.41) and chronicity of active tuberculosis (r, -0.59).
Conclusion: Patients with aàtive tuberculosis have decreased adrenocortical reserve. The adrenocortical reserve seems to be inversely related to the radiological severity of pulmonary tuberculosis and chronicity of active tuberculosis (JPMA 51:427,2001).

Introduction

Tuberculosis continues to remain the major communicable disease in the world, particularly in developing countries1. World Health Organization estimates that in 1990, 1.7 billion people were infected with tubercle bacilli, resulting in 8 million new cases each year and 2.9 million deaths every year[1,2]. The pandemic of human immune-deficiency virus infection has transformed tuberculosis, an endemic disease, into an epidemic one worldwide[2].Tuberculous involvement of the adrenal gland is well known[3-5]. It continues to be the commonest cause of Addison's disease in developing countries with high prevalence of tuberculosis[6-9]. Progressive adrenal cortical destruction must involve at least 90% of the glands before signs and symptoms of adrenal insufficiency appear[8-11]. However, in the early phases of adrenal cortical involvement, the basal serum cortisol levels may be normal, but adrenal cortical reserve will be decreased. The awareness of the existence of this so-called "pre-addisonian state" is indeed important[12].

In recent years several studies have documented decreased adrenocortical reserve in 8-58% of cases with active pulmonary as well as extra-pulmonary tuberculosis[12-19]. However a few studies have revealed normal adrenocortical reserve in patients with active tuberculosis[19,20]. Even with easy availability of antituberculous drugs, the mortality and morbidity due to tuberculosis remains significant. Reduced adrenocortical reserve could be an important factor in causing morbidity and mortality in these patients.

The present study was undertaken to document the adrenocortical reserve in patients with active tuberculosis (pulmonary as well extrapulmonary) and to study the relationship of duration and severity of disease with pattern of adrenocortical reserve.

Methods

This study was conducted on 40 patients with active tuberculosis admitted in Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir India. The purpose of the study was explained to them and an informed consent was obtained. Simultaneously, 10 healthy volunteers (age and sex matched) were also studied for their adrenocortical reserve. A detailed history was obtained from all the study subjects. This included history of cough, expectoration, hemoptysis, breathlessness, pleuritic chest pain, fever, weight loss, anorexia, weakness, vomiting, diarrhea, arthritis, urinary disturbances. Patients with past history of tuberculosis, diabetes mellitus, prolonged cortico steroid therapy, family history of tuberculosis, endocrine disease or any other auto-immune disease, malignancy and those receiving drugs like phenobarbitone, phenytoin and ketoconazole were excluded from the study. A detailed physical examination was performed in all subjects with particular reference to tuberculosis and adrenal hypofunction.

Investigations performed included hemogram with ESR, urine analysis, urea, creatinine, liver function tests, serum electrolytes and sputum/urine/pleural fluid/ascitic fluid/cerebro spinal fluid examination for acid fast bacilli (AFB). Fine needle aspiration cytology/biopsy of lymph node, pleural, peritoneum, liver or other abdominal swellings was done wherever needed. Radiology included chest x-ray, abdominal x-ray for adrenal calcification and xray spine (wherever needed). Bronchoscopy was done in selective cases.

The criteria used to diagnose active tuberculosis included sputum smear examination positive for AFB; pleural, ascitic, cerebrospinal fluid smear examination positive for AFB, urine examination positive for AFB and histopathological evidence of tuberculous granuloma. Patients with active tuberculosis were divided into two subgroups viz., active pulmonary tuberculosis and extra-pulmonary tuberculosis. Patients with active pulmonary tuberculosis had roentgenographic evidence of pulmonary infiltrates. The extent of disease was classified according to the radiological criteria of National Tuberculosis Association of USA 21, as minimal, moderately advanced and far advanced pulmonary tuberculosis. Extra-pulmonary tuberculosis comprised of patients with lymph node, peritoneal, genito-urinary and bone tuberculosis.

Adrenocorticotrophic stimulation test[15,22,24].

Basal venous blood samples (5ml), for serum cortisol estimation were drawn between 7.30 and 9.00 a.m. in all the subjects. Forty units of a depot preparation ACTFI (Acther gel; Roser Pharmaceuticals, USA) were administered intramuscularly in each subject. Venous blood samples for serum cortisol quantification were then drawn at 4, 8 and 24 hours after the basal sample. Serum cortisol estimation was done by specific radioimmunoassay using commercially available Coat-A-Count Cortisol Kit (from Diagnostic Corporation, Los Angeles).

The assessment of adrenocortical reserve in study subjects was done by interpretation of ACTH stimulation test as follows: a) Normal or adequate response, a rise of serum cortisol of >300 nmol/L above the base line; b) Inadequate response, rise in serum cortisol between 200-299 nmol/L above the

basal cortisol level and c) Negligible response, rise in serum cortisol of < 200 nmol/L above the basal cortisol level[9,11,15,16].

Statistical Analysis

Statistical Analysis was performed using the SPSS (Statistical Programme for the Social Sciences, version 6.0) software on an IBM-compatible computer. All the results unless otherwise noted are expressed as means ± SD. The comparison of serum cortisol estimates in the basal state, peak rise, maximum increase over basal (Mifi) or A rise and area under the cortisol response curves following ACTH administration between patient and cortisol groups was performed by employing students t' test and ANOVA. P values of <0.05 (two-tailed) were considered to be statistically significant.

Results

Forty cases of untreated active tuberculosis and 10 healthy control subjects completed the present study protocol.

Table 1. Clinical characteristics of patients with active tuberculosis and healthy controls.

Characteristics	Tuberculosis Group n=40	Control Group n=10	P	Remarks
1. Age (Years)				
Mean± SD	35.68±5.71	33.60±5.01	0.298	NS
Range	20-40			
2. Sex (M:F)	22 : 18	5 : 5	0.943	NS
3. Blood Pressure (mmHg)				
Sytolic				
Mean±SD	120.40±12.10	127.60±7.82	0.081	NS
Range	100-150	110-140		
Diastolic				
Mean±SD	76.3±6.10	78.40±3.24	0.301	NS
Range	70-90	70-80		

NS= Not significant, S= Significant

Table 1 gives the clinical characteristics of these subjects. The age and sex was comparable, however, the mean body mass index (BMI) of tuberculosis patients was significantly lower than that of healthy controls (P=0.016).

Table 2. Lab parameters of patients with active tuberculosis and healthy controls.

Lab parameters (Mean ±SD)	Tuberculosis Group n=40	Control Group n=10	t	P	Remarks
Hemoglobin (gm/L)	126.5±21.0	139.0±17.0	1.978	0.088	NS
ESR (mm/1st hour) (Wintrobe's method)	42.5±13.9	9.5±2.46	14.15	<0.001	S
Sodium (mmol/L)	138.32±3.46	140.30±2.36	1.989	0.094	NS
Potassium (mmol/L)	4.27±0.42	4.42±0.25	1.153	0.287	NS
Urea (mmol/L)	10.39±2.38	9.60±2.35	0.94	0.351	NS
Creatinine (μ mol/L)	75.14±24.75	79.56±10.61	0.86	0.586	NS
Bilirubin (μ mol/L)	14.88±5.64	12.83±3.93	1.34	0.285	NS
Total proteins (gm/L)	69.10±9.0	75.0±8.0	2.03	0.065	NS
Albumin (gm/L)	41.0±5.0	43.0±5.7	1.02	0.276	NS
ALP (U/L)	120.20±20.32	115±25.25	0.60	0.494	NS
SGOT (U/L)	27.92±8.30	26.51±5.50	0.65	0.614	NS
SGPT (U/L)	28.5±8.5	27.41±8.30	0.37	0.717	NS

Table 2 gives the details of hematological and biochemical parameters of tuberculosis patients and control subjects. All the hematological and biochemical parameters were comparable except erythrocyte sedimentation rate (ESR) which, understandably was higher in tuberculosis patients (P<0.001).

Out of 40 patients with tuberculosis 28 (70%) had pulmonary tuberculosis and 12 (3 0%) extrapulmonary tuberculosis. Twenty-five (89.29%) patients with pulmonary tuberculosis were AFB positive and three others had histopathological evidence of tuberculosis. Radiological extent of tuberculosis was found to be minimal lesions in 9 (32.14%), moderately advanced in 12 (42.86%) and far advanced in 7(25.0%). The extra-pulmonary tuberculosis group consisted of four pleural, three lymph node, two peritoneal, one liver, one bone and one genitourinary tuberculosis patients. Two of these patients were AFB positive and nine others had histopathologically confirmed tuberculosis.

The mean basal cortisol concentrations were comparable in the two groups. However, mean cortisol levels at 4 hours after stimulation with ACTH was significantly lower in patients with active tuberculosis as compared to healthy controls (P=0.001) as shown in Table 3.

Table 3. Mean basal and post-ACTH stimulation cortisol concerntration at 4, 8 and 24 hours between tuberculosis patients and healthy controls.

Time of estimation	Cortisol concerntration (nmol/L) Patients n=40	Controls n=10	t	P	
0 hour (Basal)	421.19±149.75	408.33±51.49	0.27	0.792	NS
4 hour	808.75±261.70	1118.75±60.55	3.69	0.001	S
8 hour	691.25±324.10	840.12±206.76	1.38	0.175	NS
24 hour	439.37±232.53	572.38±18332	1.68	0.100	NS

*Time of cortisol estimation after ACTH stimulation.

Serum cortisol rise from basal level was significant at 4, 8 and 24 hours in controls while as in tuberculosis patients such elevation was seen only at 4 and 8 hours (Table 4).

Table 4. Serum cortisol concentration before and at 4, 8, 24 hr. after depot ACTH stimulation in active tuberculosis and control groups.

Time of cortisol estimation (nmol/L)	Serum cortisol	
	Tuberculosis group n=40	Cortisol group n=10
0 hour - basal		
Mean±SD	421.19±149.75	408.33±51.49
4 hour		
Mean±SD	808.75±261.70	1118.75±60.55
Mean increase (%)*	92.02	173.98
P	<0.001 (S)	<0.001 (S)
8 hour		
Mean±SD	691.25±324.10	840.12±206.76
Mean increase (%)	64.12	105.75
P	<0.001 (S)	<0.001 (S)
24 hour		
Mean±SD	439.37±232.53	572.38±183.32
Mean increase (%)	4.32	40.18
P	0.478 (NS)	0.031 (S)

*Mean increase over basal
S: significant; NS: non-significant

Table 5. Comparison of stimulated cortisol response parameters between active tuberculosis and control groups.

Characterristics of cortisol respons	Cases n=40	Controls n=10	t	P
Maximum increase over basal (nmol/L)	414.86±187.53	710.42±61.44	4.88	<0.001 (S)
Peak rise (nmol/L)	836.05±270.68	1118.75±60.55	3.26	0.002 (S)
Area under response curve (nmol. hours/L)	14504.8±5692.0	18271.9±2815.3	2.01	0.049 (S)

Table 5 gives the details of mean maximum increase of cortisol over basal (MIB, A), peak rise of cortisol and area under response curves. All these parameters were lower in patients with active tuberculosis as compared to healthy controls (Figures 1 and 2).

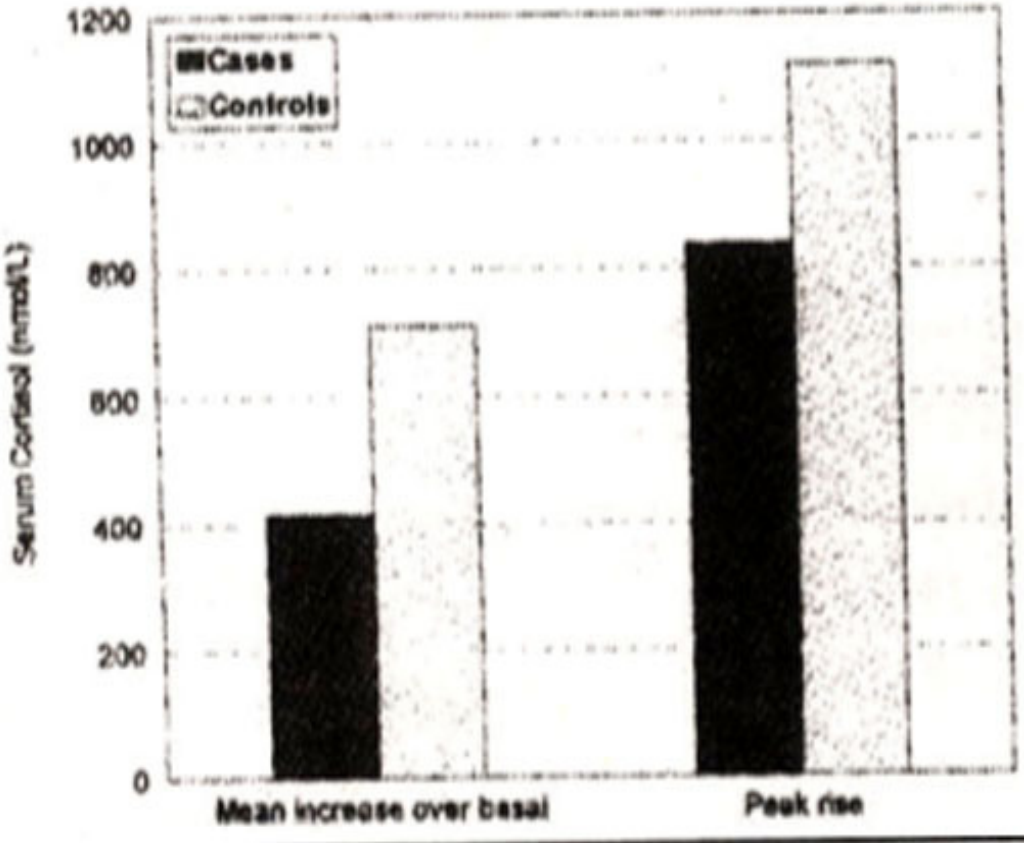

Figure 1. Stimulated cortisol response parameters tuberculosis patients versus controls.

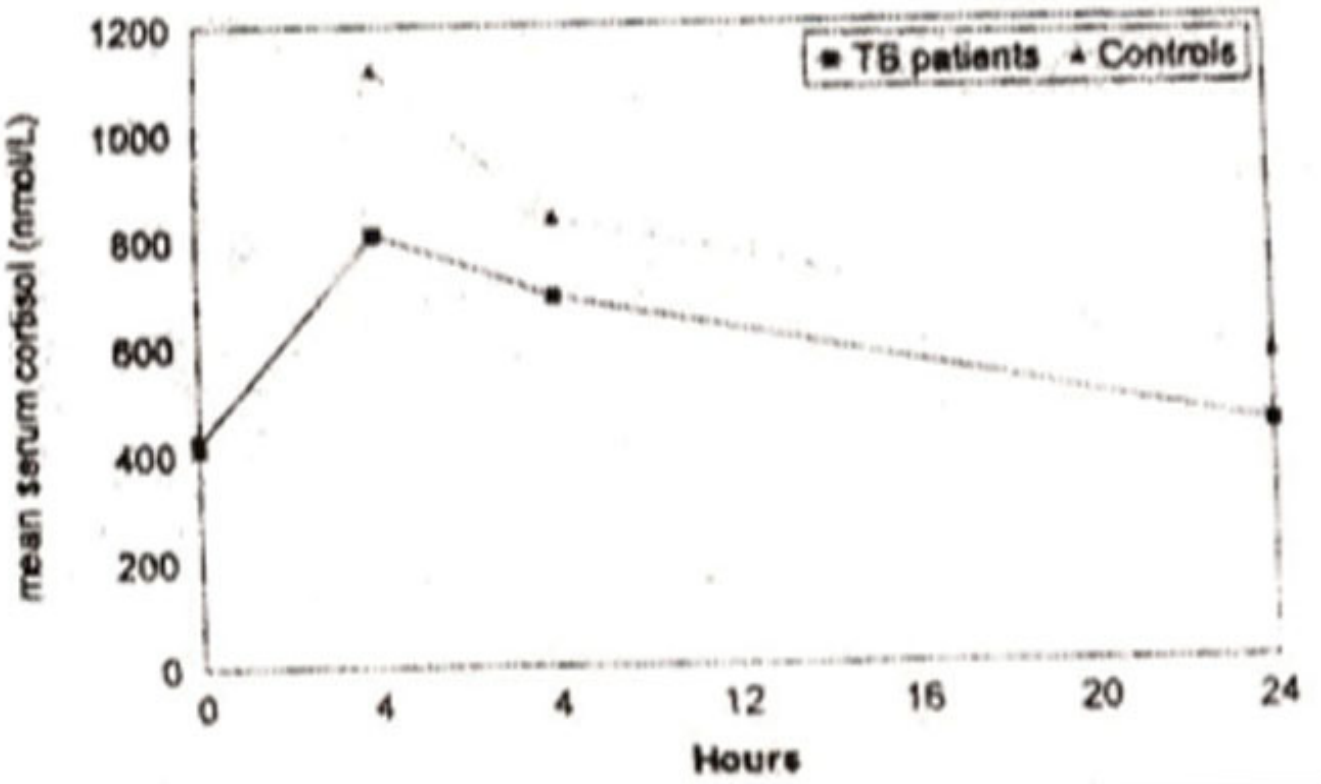

Figure 2. Area under response curve: tuberculosis patients versus controls.

The cortisol levels were comparable between pulmonary and extra-pulmonary tuberculosis patients at 0, 4, 8 and 24 hours during ACTH stimulation test (Table 6).

Table 6. Comparison of adrenal response to ACTH stimulation between pulmonary and extra tuberculosis.

Time of estimation	Serum cortisol (nmol/L) Pulmonary TB n=28	Extrapulmonary TB n=12	t	P
Basal				
0 hour	426.33±156.16*	409.18±139.38	0.33	0.745
4 hour	814.70±261.90	794.85±272.32	0.22	0.829
8 hour	695.45±321.92	681.40±343.36	0.12	0.902
24 hour	466.10±233.98	377.0±226.40	1.11	0.272

Mean±SD

Table 7. Comparison of stimulated cortisol response parameters between pulmonary and extra-pulmonary tuberculosis sub-groups.

Charactristic of cortisol response	Pulmonary TB n=32	Extra pulmonary n=8	t	P
Maximum increase over basal (nmol/L)	420.80±82.68*	401.0±206.80	0.30	0.764
Peak rise (nmol/L)	847.13±265.75	810.18±292.18	0.39	0.698
Area under response curve (nmol. hours/L)	14795.0±57650	13827.7±5708.0	0.49	0.629

Mean±SD

Table 7 gives the details of maximum increase over basal cortisol, peak rise and area under response curves in two groups of tuberculosis patients viz., pulmonary and extra-pulmonary tuberculosis. All these parameters were comparable between the two groups. Out of 40 patients with active tuberculosis, 14 (3 5%) had sub-optimal response (II inadequate and 3 negligible) and 26 (65%) had normal response to ACTH stimulation. The sub-optimal response was seen in 9 (32.14%) patients with pulmonary tuberculosis and 5 (41.67%) patients with extra-pulmonary tuberculosis (P=0.556). Among patients with pulmonary tuberculosis, 4 (66.7%) patients with advanced tuberculosis (radiologically), 4 (30.8%) patients with moderately severe tuberculosis and 1 (11.1%) patient with mild tuberculosis had sub-optimal cortisol response. This linear association of decrease in adrenal reserve with radiological severity of pulmonary tuberculosis was statistically significant (P=0.03, r = -0.41). The adrenocortical reserve appeared to be inversely related to the chronicity of active tuberculosis (P<0.001, r -0.59) as shown in Figure 3.

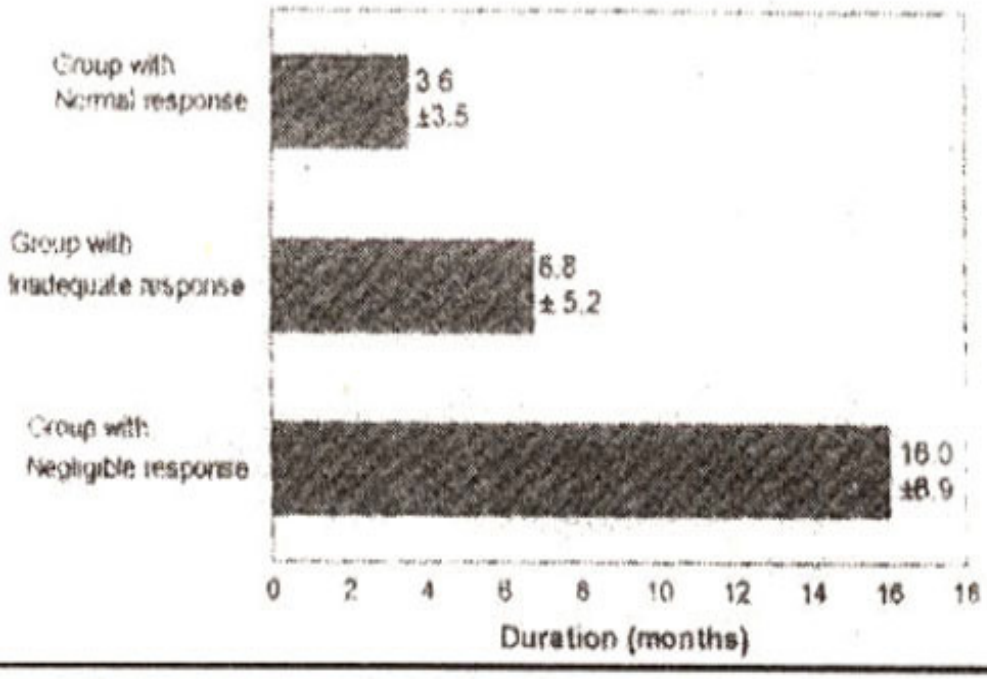

Figure 3. Adrenal gland response to ACTH stimulation in relation to duration of tuberculosis.

Discussion

In the present study adrenocortical reserve was assessed in patients with untreated active tuberculosis without any clinical evidence of Addison's disease. In order to eliminate the bias of other associated etiologies of adrenal hypoflinction, the patients with evidence of auto-immune disease, malignancy and patients taking drugs that could have interfered with adrenal function and/or cortisol metabolism were excluded from the study. The mean BMI of patients with tuberculosis was significantly lower than that of healthy controls. However, there was no significant difference in BMI between patients with sub-optimal and normal cortisol response to ACTH stimulation. These observations are in agreement with that of Mugusi et a1[16]. and Shuster et al[25] and most likely speak of the debilitating nature of the tuberculosis itself rather than that of adrenal hypofunction.

Tuberculosis is a major communicable disease the world over and an important health problem in India. The strong association between tuberculosis and human immunodeficiency virus (HIV) infection had led to an upsurge of tuberculous worldwide. Contradictory reports on adrenocortical status in patients suffering from tuberculosis and paucity of reports from our country, prompted us to conduct this study.

Many studies conducted in the past have revealed adrenal tuberculosis as an important etiology of Addison's disease[3,5,7,26,27]. In a recent study from India, 5 patients with adrenal tuberculosis causing. Addison's disease were followed and it was documented that treatment with antituberculous chemotherapy does not lead to normalization of adrenal functions[28]. The existence of an addisonian like syndrome with anatomically normal adrenal glands (functional hypoadrenalism) has been reported in patients with untreated active tuberculosis[14,15,22,29]. However, few studies have also revealed decreased pituitary ACTH reserve and hence secondary hypo-adrenalism[25,30-32].

In the present study, on ACTH stimulation, 35% of patients with active tuberculosis had sub-optima! cortisol response. The sub-optimal response was seen in 9 (32.14%) patients with pulmonary tuberculosis and 5 (41.67%) patients with extra-pulmonary tuberculosis. However, this difference was

not statistically significant. Various studies have reported a sub-optimal cortisol response in 31-51% of patients with active tuberculosis[15-17]. Contrary to present observations of decreased adrenocortical reserve, few studies have reported normal adrenal cortex reserve in patients with active tuberculosis[19,20,33]. A recent study on 50 patients with active pulmonary tuberculosis did not document any evidence of hypocortisol state[34]. Contrary to the finding of present study, Barnes et al observed suboptimal cortisol response more frequently in extra-pulmonary tuberculosis as compared to pulmonary tuberculosis[14].

The mean basal cortisol level was slightly but not significantly higher in active tuberculosis patients. These results are in agreement with few earlier studies[15,16,18,32]. In order to compare the adrenocortical reserve between patients with active tuberculosis and healthy controls, parameters of stimulated cortisol response including maximum increase of cortisol over basal level, the peak rise of cortisol and area under response curve were assessed. In the present study, the mean maximum increase of cortisol over basal level, peak rise of cortisol and area under response curves were significantly lower in patients with active tuberculosis than those of healthy controls. These parameters were comparable in the two subgroups of active pulmonary and extra-pulmonary tuberculosis. These findings. strongly indicate that the overall response of adrenal glands to ACTH is blunted in patients with active tuberculosis and these hypofunctional adrenal glands may even fail to mount a required response during the periods of stress like trauma or superadded acute infections. Despite the decreased reserve, the normal basal cortisol concentration (in fact slightly higher levels) is maintained by these functionally impaired glands due to continuous stimulation by ACTH released from the pituitary gland as a result of stress of chronic infection. Most of the earlier studies have not calculated these important parameters, instead have relied on single cortisol estimations following ACTH stimulation[13,14,32,33], obviously is a poor indicator of adrenal cortical reserve.

The study of the pattern of serum cortisol response with respect to time following depot ACTH stimulation revealed that significant cortisol rise in patients with active tuberculosis was observed at 4 and 8 hours only, while as in healthy controls the cortisol rise was more prolonged and continued up to 24 hours. It is also worth noting that the mean cortisol response at 4 hours was significantly lower in patients with active tuberculosis as compared to healthy controls ($P<0.001$). The cortisol response to ACTH with respect to time was comparable between active pulmonary and extra-pulmonary tuberculosis subgroups. From these observations it is clear that adrenal glands of patients with active tuberculosis fail to maintain prolonged cortisol response to depot ACTH stimulation as compared to healthy controls where adrenal glands respond more briskly and for prolonged periods.

The relationship of adrenal response with radiological severity of pulmonary disease revealed that sub-optimal cortisol response to ACTH was more frequently observed in patients with far-advanced tuberculosis (66.7%) than those with minimal lesion tuberculosis (11.11%). These observations are consistent with an earlier study[19]. The present study documented that duration of active tuberculosis was inversely related to the adrenocortical reserve. Patients with negligible cortisol response to ACTH had the longest mean duration of active disease. The difference in duration of active disease among patients with normal, negligible and inadequate cortisol response to ACTH was statistically significant.

In conclusion, we have demonstrated normal basal cortisol levels in most of the patients with active tuberculosis; the response to depot ACTH stimulation at 4 hours even though adequate is greater in normal controls and the response does not last for 24 hours as in healthy controls. Adrenal cortical reserve in active tuberculosis is decreased as determined by maximum increase of cortisol over basal, peak rise of cortical and area under response curve after depot ACTH stimulation. The, extent of adrenal hypofunction is directly correlated with duration of the disease.

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