

ORIGINAL RESEARCH REPORT

# The adrenal gland and the patient with pulmonary tuberculosis infected with human immunodeficiency virus

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## ABSTRACT

**Background:** The adrenal gland is not spared from the involvement by tuberculosis. One of the recognized causes of adrenal insufficiency (AI) is tuberculosis. AI, mostly at the subclinical level, is common in persons with pulmonary tuberculosis (PTB) infection, occurring in about 23% of patients. Coinfection with PTB and human immunodeficiency virus (HIV) may compromise adrenocortical function and produce significant adrenocortical insufficiency. **Objective:** To determine if coinfection with tuberculosis and HIV have a compound effect on adrenocortical function in persons with HIV and PTB coinfection. **Materials and Methods:** Persons with sputum-positive PTB, treatment naive, who met our inclusion criteria, were selected. All the recruited patients were screened for HIV and those positive for HIV infection had confirmatory test. A baseline blood samples for cortisol, fasting plasma glucose, full blood count, and electrolytes were collected between 8.00 h and 9.00 h immediately before administration of adrenocorticotrophic hormone (ACTH). The persons received an intravenous bolus injection of 1 µg ACTH (Alliance Pharmaceuticals Ltd., Chippenham, Wiltshire SN15 2BB) and blood sample was drawn for cortisol level at 30 min. **Results:** Forty-four people with PTB infection and forty people with PTB and HIV coinfection met the inclusion criteria of the study. The adrenal response to 1 µg ACTH stimulation in participants with PTB and PTB and HIV coinfection showed that the mean basal cortisol level in the 2 groups was not statistically significant; however, 30-min post-ACTH stimulation cortisol level was  $630.84 \pm 372.17$  and  $980.36 \pm 344.82$  nmol/L ( $P < 0.001$ ) and increment was  $367.79 \pm 334.87$  and  $740.77 \pm 317.97$  nmol/L ( $P < 0.001$ ), respectively. Fourteen persons (31.8%) with PTB has subnormal adrenal response to ACTH stimulation while only 2 (5%) persons with PTB and HIV coinfection has subnormal response. **Conclusion:** AI, at subclinical level, was less frequent in those with PTB and HIV co-infection.

**Key words:** Adrenal gland, adrenocortical insufficiency, human immunodeficiency virus, pulmonary tuberculosis

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## INTRODUCTION

The adrenal gland, as studies have shown, is not spared from the involvement by tuberculosis.<sup>[1,2]</sup> One of the recognized causes of adrenal insufficiency (AI) is tuberculosis.<sup>[3]</sup> Impaired cortisol response to dynamic testing of the adrenal glands with synacthen has been found in patients with tuberculosis

with varying prevalence of adrenocortical insufficiency in these studies.<sup>[4-8]</sup> A study from Nigeria showed that adrenocortical insufficiency, mostly at the subclinical level, is common in persons with pulmonary tuberculosis (PTB) infection, occurring in about 23% of patients.<sup>[4]</sup>

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Adrenal gland involvement has been documented in as many as two-thirds of patients with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) at postmortem examination.<sup>[9]</sup> AI secondary to HIV infection has been well studied. Only a few cases of clinically significant primary AI have been reported in persons with HIV infection although a prevalence of 22% was reported by Piédrola *et al.*<sup>[10]</sup> while a prevalence of 35% was reported in a study from Nigeria.<sup>[11]</sup> Freda *et al.* found primary AI in six hospitalized patients with AIDS.<sup>[12,13]</sup>

In many developing countries, tuberculosis has emerged as the most common opportunistic infection associated with HIV infection.<sup>[14]</sup> Mortality is increased in HIV-infected patients with tuberculosis.<sup>[14]</sup> Coinfection with tuberculosis and HIV may compromise adrenocortical function and produce significant adrenocortical insufficiency. The objective of this study is to determine if coinfection with tuberculosis and HIV have a compound effect on adrenocortical function in persons with PTB and HIV coinfection.

## MATERIALS AND METHODS

Consecutively presenting persons with sputum-positive PTB, treatment naive, who met our inclusion criteria, were selected for the study. Other inclusion criteria include participants who are 18 years and above and are newly diagnosed with PTB. All the recruited patients were screened for HIV infection using enzyme-linked immunosorbent assay (ELISA method). Those found positive for HIV infection were subsequently confirmed using immunoelectrotransfer blot (Western blot). Pregnant women, people with diabetes mellitus, and individuals on medicines known to affect adrenocortical function (examples are steroid, anticonvulsants, and antifungal medications) were excluded from the study. The patients were recruited from the Lagos University Teaching Hospital (LUTH). Informed consent was obtained from all persons and the LUTH Ethics and Research Committee approved the study.

A data collection sheet, filled by the investigator, was used to obtain information from the subjects. Information obtained from each participant included the biodata, presence of weakness, fatigue, cough, hemoptysis, fever, weight loss, anorexia, nausea, vomiting, diarrhea, and a history of glucocorticoid and/or antiretroviral drug use.

The study groups were divided into batches of ten persons each. The participants arrived on the assigned day at the laboratory, 60 min before the adrenocorticotrophic hormone (ACTH) testing, after an overnight fast of 8–10 h. Physical examination including pulse rate and blood pressure in supine and erect position was performed. A venous access kept patent with heparinized saline was secured. The participants then rested for 30 min after securing the venous access before samples were collected.

Each patient then received 1 µg of tetracosactrin acetate corticotropin (Synacthen®) intravenously. Low-dose 1 µg short Synacthen® test was previously validated against the 250 µg Synacthen® test.<sup>[15]</sup> A baseline blood samples for cortisol, fasting plasma glucose, full blood count, and electrolytes were collected immediately before administration of Synacthen®. ACTH testing was conducted between 8.00 h and 9.00 h. After the samples had been collected, the patient received an intravenous bolus injection of 1 µg Synacthen® (Alliance Pharmaceuticals Ltd., Chippenham, Wiltshire SN15 2BB). After the bolus was administered, blood sample was drawn for cortisol level at 30 min. The samples were separated and transported on an ice slab to the laboratory where the plasma was stored at –20°C until assayed.

PTB was diagnosed using sputum positive for acid and alcohol fast bacilli (AAFB) using Ziehl–Neelsen stain. HIV infection was diagnosed if screened positive by ELISA method using AccuDiag®-HIV 1, 2 ELISA (Diagnostic Automation/Cortez Diagnostics, Inc., Woodland Hills, California 91367 USA) and confirmed by immunoelectrotransfer blot (Western blot).<sup>[16]</sup>

A normal response to 1 µg ACTH stimulation has previously been published.<sup>[11]</sup> AI in this study was defined as 30 min cortisol level <380.2 nmol/L and increment from basal to stimulated cortisol level <158.5 nmol/L.

## Assay

Serum cortisol levels were determined by an ELISA technique using the Diagnostic automation Inc., cortisol assay method. It is a competitive immunoenzymatic colorimetric method for quantitative determination of cortisol concentration in serum. The respective intra-assay and inter-assay coefficients of variation of 4.5% and 3.1% for serum cortisol were within the acceptable range of variation.

## Statistical analysis

Calculations and analysis were done using the SPSS 19.0 software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, IBM Corp. Version 19.0. Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation. Student's *t*-test was used for the comparison of means between two groups. Chi-square test was used for comparison of proportions between two groups. Pearson's correlation coefficient analysis was used to determine associations between body mass index (BMI) and cortisol level. The level of statistical significance was taken as  $P < 0.05$ .

## RESULTS

### Study population

One hundred sputum positive for AAFB and treatment-naive people with PTB were recruited for the study. Fifty-four of the people with PTB were HIV negative while 46 of the

people with PTB were HIV positive. Ten out of the 54 people with PTB infection only were excluded from the study because they were already on medications for PTB which were stopped just before presenting to LUTH. HIV infection was not confirmed in two of the 46 people with PTB and HIV coinfection while four of the remaining 44 with PTB and HIV coinfection were excluded from the study because they declined further participation in the study.

The clinical characteristics of the study participants are shown in Table 1. They were quite similar, except for a significant difference in BMI and weight in the participants with PTB only and the participants with PTB and HIV coinfection.

### Adrenal function

The adrenal response to 1 µg ACTH stimulation in participants with PTB and PTB and HIV coinfection is shown in Table 2. The mean basal cortisol level in the two groups was not statistically significant; however, 30 min post-ACTH stimulation cortisol level and increment were significantly lower in participants with PTB than in participants with PTB and HIV coinfection.

### Frequency of adrenal insufficiency

The frequency of AI in the study participants, using the diagnostic criteria set for this study, is shown in Table 3. Fourteen persons (31.8%) out of 44 of those with PTB have subnormal adrenal response to ACTH stimulation while only 2 (5%) persons with PTB and HIV coinfection have subnormal response. This was statistically significant.

### Biochemical parameters in study participants

There was no significant difference in the biochemical parameters in the PTB and PTB and HIV coinfection [Table 4].

## DISCUSSION

The adrenal cortex is a common site of pathological involvement in patients with PTB and patients with PTB and HIV coinfection. Detection of impaired adrenocortical function is of potential relevance as cortisol deficiency could account for unexpected deaths seen occasionally in patients with PTB, HIV, or both.<sup>[17]</sup>

The mean basal cortisol level was comparable in patients with PTB and patients with PTB and HIV coinfection. This finding suggests that infiltration of the adrenal gland by the tuberculous process and HIV infection does not occur to a sufficient degree to cause a clinically significant deficit. The amount of adrenal gland tissue remaining functional, however, is apparently enough to provide a satisfactory glucocorticoid production in the basal state.

This study demonstrated an impaired stimulated cortisol response to the 30 min synacthen stimulation test in a significant proportion of patients with tuberculosis. This

is in keeping with the findings of previous studies.<sup>[6,8,18]</sup> Two studies from Nigeria demonstrated adrenocortical insufficiency, mostly at the subclinical level, in persons with HIV infection and PTB infection, occurring in about 34% and 23% of patients, respectively.<sup>[4,11]</sup> We thus expect that coinfection with PTB and HIV should have an additive effect on the impaired stimulated cortisol response to the 30 min synacthen stimulation test. However, in this study, 14 persons (31.8%) out of 44 of those with PTB have subnormal adrenal response to ACTH stimulation while only 2 (5%) persons with PTB and HIV coinfection have subnormal response. The finding in this study was

**Table 1: Clinical characteristic of the participants**

Parameters	Diagnosis, mean (SD)		P
	PTB (n=44)	PTB + HIV (n=40)	
Age (years)	34.39 (11.27)	37.53 (11.06)	0.202
BMI (kg/m <sup>2</sup> )	18.89 (2.91)	21.77 (2.60)	0.000
Weight (kg)	52.87 (10.02)	58.95 (8.41)	0.004
SSBP (mmHg)	110.45 (13.11)	116.05 (19.33)	0.122
SDBP (mmHg)	70.0 (8.06)	72.8 (12.96)	0.234
ESBP (mmHg)	111.50 (13.82)	114.80 (19.49)	0.370
EDBP (mmHg)	70.82 (7.93)	74.05 (12.39)	0.155

PTB=Pulmonary tuberculosis, HIV=Human immunodeficiency virus, SD=Standard deviation, SSBP=Supine systolic blood pressure, SDBP=Supine diastolic blood pressure, ESBP=Erect systolic blood pressure, EDBP=Erect diastolic blood pressure, BMI=Body mass index

**Table 2: Serum cortisol level in response to adrenocorticotrophic hormone stimulation in study participants**

Time of sampling	Serum cortisol level, mean (SD)		P
	PTB (n=44)	PTB + HIV (n=40)	
Basal, 0 min (mmol/L)	263.04 (122.96)	239.58 (84.62)	0.316
Stimulated, 30 min (mmol/L)	630.84 (372.17)	980.36 (344.82)	0.000
Increment (mmol/L)	367.79 (334.87)	740.77 (317.97)	0.000

PTB=Pulmonary tuberculosis, HIV=Human immunodeficiency virus, SD=Standard deviation

**Table 3: Frequency of adrenocortical insufficiency in participants**

Diagnostic criteria (stimulated cortisol level and increment)	Participants, n (%)	
	PTB (n=44)	PTB + HIV (n=40)
<380.2+<158.5	14 (31.8)	2 (5.0)
≥380.2+≥158.5	30 (68.2)	38 (95.0)

χ<sup>2</sup>=9.77, P=0.002. PTB=Pulmonary tuberculosis, HIV=Human immunodeficiency virus

**Table 4: Biochemical parameters in study participants**

Analyte	PTB, mean (SD)	PTB + HIV, mean (SD)	P
Sodium	136 (2.78)	137.32 (2.8)	0.94
Potassium	3.70 (0.50)	3.8 (0.36)	0.06
Urea	18.32 (5.5)	18.93 (6.3)	0.14
FPG	5.7 (1.3)	5.3 (0.78)	0.31

PTB=Pulmonary tuberculosis, HIV=Human immunodeficiency virus, FPG=Fasting plasma glucose, SD=Standard deviation

similar to finding of a study by Kaplan *et al.* done in South Africa.<sup>[19]</sup> Kaplan *et al.* reported that persons with HIV/PTB had a higher response to ACTH compared with persons with HIV and PTB alone. They also demonstrated that AI was not common in patients with HIV and PTB.<sup>[19]</sup> They found that only 1 (4.5%) person out of 22 with HIV and PTB have adrenocortical insufficiency. It is however difficult to explain the higher stimulated cortisol response seen in patients with PTB and HIV coinfection and the low proportion with subnormal adrenal response to ACTH stimulation. Proposed mechanisms for this hypercortisolemia include a shift in steroidogenesis from dehydroepiandrosterone and aldosterone to cortisol and the stimulation of hypothalamus, pituitary, and adrenal cortex by cytokines.<sup>[20,21]</sup> Moreover, the stimulation of the hypothalamic-pituitary-adrenal axis may also result from the stimulatory effects of viral proteins. CD4 count does not predict the presence or absence of adrenocortical insufficiency. It cannot be used to diagnose adrenocortical function.<sup>[22]</sup>

The mean systolic or diastolic blood pressure was comparable in the PTB and the PTB and HIV coinfection groups and also in those with impaired serum cortisol response. This is in keeping with studies done in Kenya and South Africa.<sup>[23-25]</sup>

The biochemical parameters [Table 4] were similar in both groups. Those with impaired cortisol response had glucose level within the acceptable range. The normoglycemia seen in them is explained by their normal basal cortisol level.<sup>[9,19]</sup>

The mineralocorticoids are under the control of the renin-angiotensin system. This system is probably intact in people with PTB and PTB and HIV coinfection. Furthermore, the functional gland remaining is adequate for mineralocorticoid production.<sup>[9,19]</sup>

## CONCLUSION

An impaired cortisol response is common in PTB but less prevalent in PTB and HIV coinfection.

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## Conflicts of interest

There are no conflicts of interest.

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