

Serum IgE levels of tuberculosis patients in a tropical setup with high prevalence of HIV and intestinal parasitoses

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SUMMARY

Tuberculosis remains a major health problem worldwide in the era of HIV/AIDS. Co-infection with intestinal parasites has been suggested to worsen the outcome of infection by polarizing the immune response towards Th2. This study investigated serum IgE levels of 241 tuberculosis patients and compared the IgE profiles in the tuberculosis patients either with or without intestinal helminthic infection and/or HIV infection. The serum levels of IgE in tuberculosis patients before initiation of antimycobacterial chemotherapy were found to be 1722 ± 1290 IU/ml (Mean $\pm$ SD) in HIV seronegatives and 2366 ± 1849 IU/ml in HIV seropositives. Further, the IgE level was significantly higher in patients coinfected with intestinal helminthes and HIV compared to those infected with helminthes or without coinfection ($P < 0.05$). Anti-tuberculosis chemotherapy significantly reduced serum IgE levels in HIV seronegative tuberculosis patients ($P < 0.05$). These findings might indicate an active role of therapy in shifting the immune response towards Th1 which is crucial for prognosis in tuberculosis patients.

Keywords tuberculosis HIV intestinal helminthes TH2 IgE Ethiopia

INTRODUCTION

Tuberculosis (TB) remains one of the most common and deadliest infectious diseases worldwide. An estimated number of 8.3 million new cases and 1.8 million deaths occurred in the year 2000 [1]. More than 95% of these figures were from developing countries [1]. The sub-Saharan Africa had by far the highest annual incidence rate fuelled by the high prevalence of human immunodeficiency virus (HIV) [1].

It has been well-established that the patterns of released cytokines during specific immune responses are characteristic for distinct subsets of CD4⁺ T helper (Th) cells, whose polarized forms are Th1 and Th2 [2]. Th1 cells produce IFN- γ but not IL-4, express cytotoxicity, activate macrophages and promote cell-mediated immunity. Th2 cells, on the other hand, secrete IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, but not IFN- γ , induce B cell differentiation with production of all immunoglobulin isotypes

including IgE, and inhibit several macrophage functions. However, most of CD4⁺ Th cells express a mixed pattern, designated as Th0, that exert intermediate effects depending on the ratio of cytokines produced and the nature of responding cells [3]. Differentiation of the Th0 cells into Th1 and Th2 is biased by antigen dose and its structure, the concurrence of distinct costimulatory molecules, the kind of cells presenting the antigenic peptides, and the presence of particular cytokines in the microenvironment [3].

Infection with intracellular parasites such as *Mycobacterium tuberculosis* induces Th1 immune response whereas intestinal parasites, mainly helminthes, elicit Th2 immune response. In sub-Saharan Africa, where the prevalence of parasitic infections is very high, a dominant Th2 polarized immune response has been reported [4] and suggested to increase susceptibility to both *M. tuberculosis* and HIV. Co-infection also hastens progression of their disease [5–7]. Such an imbalance with an increase in Th2 cells favours IgE production [3] which may have clinical effects such as poor prognosis in coinfecting individuals.

There have been no immunological reports on interactions between TB, intestinal parasitoses and HIV in Ethiopia, a country in sub-Saharan Africa where the prevalence of these infections is very high [1,8,9]. Therefore, this study aimed to investigate the IgE profile *in vivo*, as a measure of Th2 immune response, in TB

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patients with or without HIV and/or intestinal parasites coinfection at the time of diagnosis and after completion of an intensive phase of anti-TB chemotherapy.

PATIENTS AND METHODS

Study subjects and area

Subjects examined were consecutive TB patients visiting the Gondar University College Hospital between January 2003 and August 2003. It is a tertiary level teaching and referral hospital catering 400 beds for inpatients and rendering referral health services for over 4 million inhabitants in the North-west Ethiopia. Patients were included in the study only after getting an informed consent. The study was approved by the research ethics committee of the University College.

Diagnosis and treatment of tuberculosis

Diagnosis of TB was made combining two or more of the following:

- positive sputum smear;
- histopathological evidence;
- radiographic examination consistent with TB;
- clinical response to anti-TB chemotherapy.

For patients without bacteriological or histological evidence of TB, a two week trial therapy with a broad spectrum antibiotic was attempted before considering for TB chemotherapy. After TB diagnosis, all patients received directly observed therapy short course (DOTS) with isoniazid, pyrazinamide, rifampicin, and ethambutol or streptomycin for eight weeks followed by continuation phase of six months with isoniazid and ethambutol as per the protocol of the National Tuberculosis and Leprosy Prevention and Control Programme [10]. All HIV infected TB patients were naïve to antiretroviral drugs.

Stool examination

Stool samples were collected and examined on three consecutive days by direct microscopy of samples in saline and iodine. Formalin-ether sedimentation concentration methods were also followed to detect the intestinal parasites [11]. Patients found positive for intestinal protozoa (*Entamoeba histolytica* and *Giardia lamblia*) were treated with metronidazole or tinidazole. However, such patients were excluded from the study as IgE response is different in protozoal infection than in worm infections. Subjects found positive for intestinal helminthes were treated with broad spectrum anthelmintics such as mebendazole, praziquantel, thiabendazole, and niclosamide where appropriate. These patients were then followed up during therapy and stool samples were obtained and re-examined at the end of intensive phase of anti-TB chemotherapy. Those successfully treated for intestinal helminthes and found negative for them two months after chemotherapy were selected to study the effect of anthelmintic treatment.

Blood collection and screening for HIV

After appropriate pretest counseling, venous blood was collected from each patient before initiation of therapy, and in a sub sample of them at the end of intensive phase of anti-TB chemotherapy. Serum was separated by centrifugation within two hours of collection and kept at -20°C until used. The presence of HIV antibodies was determined by an enzyme linked immunosorbent

assay following the manufacturer's instruction (Vironostica HIV Uni-Form II plus O, Organon Teknika, Boxtel, the Netherlands).

Serum IgE determination

The serum IgE levels were quantified by total IgE ELISA kit (IBL Immunobiological Laboratories, Hamburg, Germany) following the manufacturer's instructions. In brief, 10 μl serum samples or standard IgE were pipetted in duplicates into wells of microtiter plates precoated with monoclonal mouse antihuman IgE antibody together with peroxidase conjugated antihuman IgE. After incubation for 30 min at room temperature the plates were rinsed with diluted wash buffer to remove unbound material. Then a substrate solution (tetramethylbenzidine) was pipetted and incubated for 15 min to induce development of colour. The reaction was terminated by the addition of stop solution and the resulting dye was measured in a spectrophotometer (Model 680 Microplate Reader, Bio-Rad Laboratories Inc., Japan) at a wave length of 450 nm against the substrate blank. The IgE concentration of the samples was read from a standard curve. Mean values of two separate determinations from each sample was used as serum IgE level of a particular study subject.

Statistical analysis

The data were analysed using SPSS version 10 statistical package. Results are reported as Means and Standard Deviations from the Means. Mean IgE values were compared by the students *T*-test. The non parametric Wilcoxon matched-pair signed-rank test was used to compare paired data. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Two hundred and forty-one TB patients were included in the study. Table 1 shows demographic and clinical data of the

Table 1. Demographic and clinical data of TB patients included in the study by HIV status ($n = 251$)

Parameter	HIV status	
	HIV- ($n = 117$) n (%)	HIV+ ($n = 124$) n (%)
Age		
< 40	83 (70.9)	104 (83.9)
≥ 40	34 (29.1)	20 (16.1)
Sex		
Male	45 (38.5)	52 (41.9)
Female	72 (61.5)	72 (58.1)
TB type		
Pulmonary	44 (37.6)	53 (42.7)
Extrapulmonary	73 (62.4)	71 (57.3)
Intestinal parasites		
Positive	48 (41.0)	42 (33.9)
Negative	69 (59.0)	82 (66.1)
Mean IgE†		
Baseline	1723 $\pm$ 1291	2366 $\pm$ 1849
Follow up	1061 $\pm$ 780*	2408 $\pm$ 2095**

* $n = 25$, ** $n = 31$, †mean $\pm$ SD.

patients. Majority of the patients were females (59.1%). 76.5% of the patients were younger than 40 years old. One hundred and twenty four (51.4%) of the TB patients were seropositive for HIV. Pulmonary and extrapulmonary tuberculosis were diagnosed in 40.3% and 59.4% of the patients, respectively. Intestinal helminthic parasites were detected in 42 (33.9%) of the 124 HIV seropositive and 48 (41%) of the 117 HIV seronegative TB patients. The prevalence and type of intestinal helminthes detected in the patients is shown in Table 2.

Mean IgE concentration found in HIV positive TB patients (Mean $\pm$ SD, 2366 $\pm$ 1849) was significantly higher than in HIV negative TB patients (Mean $\pm$ SD, 1723 $\pm$ 1291), $P < 0.001$ (Table 1). It was significantly higher in patients with intestinal helminthic parasites than in those without intestinal helminthes in HIV seronegative TB patients, $P = 0.038$ (Fig. 1). This difference was not significant in HIV seropositive TB patients, $P = 0.2$. The IgE values progressively increased from patients negative for both HIV and intestinal helminthes (Mean $\pm$ SD, 1547 $\pm$ 1176) to those positive for either intestinal helminthes (Mean $\pm$ SD, 1976 $\pm$ 1412) or HIV (Mean $\pm$ SD, 2279 $\pm$ 1767) and finally to

Table 2. Type and frequency of intestinal helminthes in TB patients by HIV status

Parasite	HIV status	
	HIV- <i>n</i> (%)	HIV+ <i>n</i> (%)
<i>Ascaris lumbricoides</i>	26 (43.3)	19 (38.0)
Hookworm	18 (30.0)	8 (16.0)
<i>Strongyloides stercoralis</i>	8 (13.3)	14 (28.0)
<i>Schistosoma mansoni</i>	4 (6.7)	8 (16.0)
<i>Trichuris trichiura</i>	2 (3.3)	0 (0.0)
<i>Hymenolepis nana</i>	1 (1.7)	0 (0.0)
<i>Enterobius vermicularis</i>	1 (1.7)	0 (0.0)
<i>Taenia saginata</i>	0 (0.0)	1 (2.0)

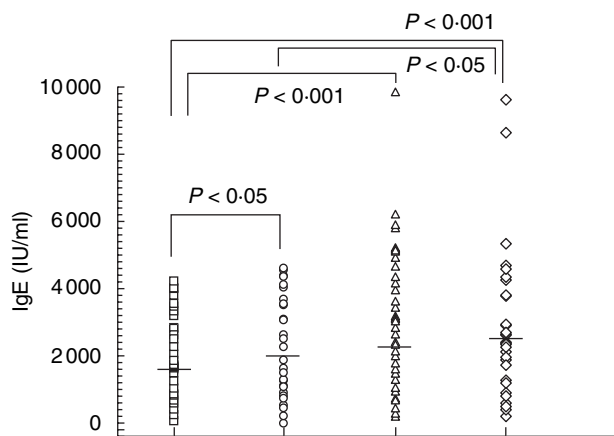


Fig. 1. Serum IgE levels in adult TB patients before initiation of anti-TB chemotherapy. Individual values are presented with the horizontal lines showing mean values. IgE profile of HIV seronegative TB patients without ($\square$, $n = 69$) and with ($\circ$, $n = 48$) intestinal helminthes infection and HIV seropositive TB patients without (Δ , $n = 82$) and with ($\diamond$, $n = 42$) intestinal helminthes infections, respectively.

those with both HIV and helminthes (Mean $\pm$ SD, 2538 $\pm$ 2012) (Fig. 1).

In 20 HIV seronegative and 20 HIV positive TB patients, who were negative for intestinal parasitic infections at baseline and at the end of intensive phase of anti-TB chemotherapy, effect of anti-TB chemotherapy on the profile of IgE was studied. As shown in Fig. 2, there was a significant reduction in serum IgE concentration at the end of the intensive phase of anti-TB chemotherapy in HIV seronegative TB patients compared to its level before initiation of therapy (Mean $\pm$ SD, 1646 $\pm$ 1309 versus 1023 $\pm$ 838, $P = 0.003$). A decline in serum IgE was also observed at the end of the intensive phase chemotherapy in HIV positive TB patients but the difference was not statistically significant (Mean $\pm$ SD, 2530 $\pm$ 1639 versus 2300 $\pm$ 2275, $P = 0.2$) (Fig. 2). However, a significant decline in IgE, after treatment, was noted in HIV positive patients with pulmonary tuberculosis (Mean $\pm$ SD, 3281 $\pm$ 2064 versus 2345 $\pm$ 1905, $P = 0.03$) unlike patients with extrapulmonary tuberculosis, where a remarkable increase in IgE was observed (Mean $\pm$ SD, 1878 $\pm$ 1605 versus 2496 $\pm$ 2411, $P = 0.07$).

In a subset of HIV seronegative TB patients who were positive for intestinal helminthes during diagnosis of TB and successfully treated by antiparasitic agents, a significant decline in IgE level (Mean $\pm$ SD, 2140 $\pm$ 1258 versus 1214 $\pm$ 684, $P = 0.04$, $n = 5$) eight weeks after therapy was observed (Fig. 3). On the contrary, the difference was not significant in sub sample of HIV positive TB patients who were also treated for intestinal helminthes, although a decline was noted (Mean $\pm$ SD, 2990 $\pm$ 2563 versus 2604 $\pm$ 1807, $P = 0.3$, $n = 11$) (Fig. 3).

DISCUSSION

The immune profile of individuals living in sub Saharan Africa is characterized by a background of chronic immune activation which has been attributed to exposure to high load of environmental antigens [4–7]. Such exposure has been suggested to impair the host's immune response to HIV and *M. tuberculosis* [5] which are highly prevalent in that part of the world [1].

The present study was conducted in a tropical country, in sub Saharan Africa, where the prevalence of intestinal parasites, HIV

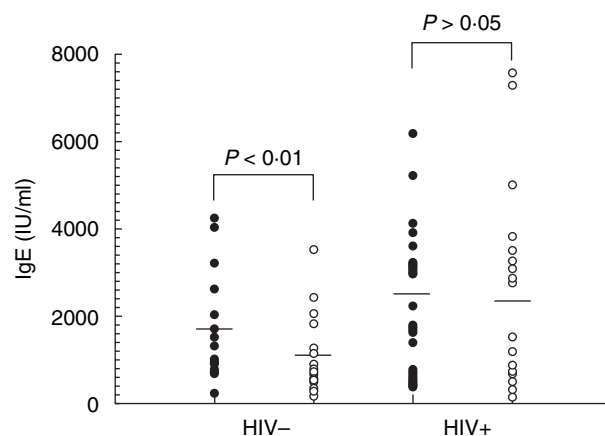


Fig. 2. Serum IgE levels in adult HIV- ($n = 20$) and HIV+ ($n = 20$) TB patients, who were free from intestinal parasitic infections, during diagnosis ($\bullet$) and two months after anti-TB chemotherapy ($\circ$). Individual values are presented with horizontal lines showing mean values.

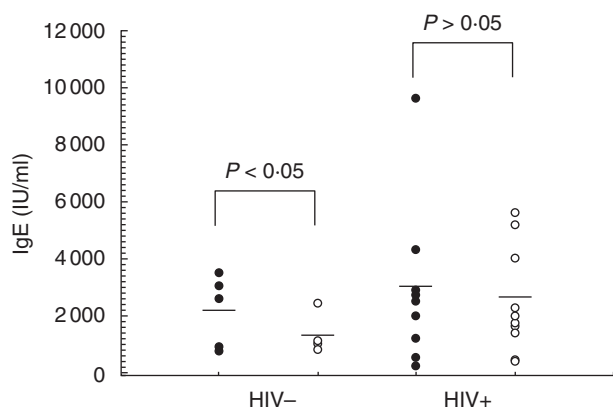


Fig. 3. Serum IgE levels in adult HIV- ($n = 5$) and HIV+ ($n = 11$) TB patients with intestinal helminthic infection (●) and two months after treatment (○) for the parasites and TB. Individual values are presented with horizontal lines showing mean values.

and TB is amongst the highest in the world [1,8,9]. Interestingly, this study was the first of its kind to report the effect of the triple coinfection on serum IgE levels. The results of the study indicated that the level of serum IgE was remarkably high in TB patients. In addition it was revealed that serum IgE was higher in patients coinfecting with HIV and/or intestinal parasites compared to that in the subjects with TB only. Elevated IgE levels from untreated TB patients were reported previously indicating an *in vivo* evidence for Th2 activation in the patients [12–18]. Likewise, increased IgE levels were reported in HIV infected subjects indicating an abnormal T cell regulation of antibody synthesis by B cells [19–25].

The highly elevated IgE profile in TB patients with HIV coinfection might be a result of HIV induced immune dysregulation which induces shift in cytokine production from Th1 to Th2 [26] and the resulting polyclonal activation of B cells [27]. The production of cytokines including IL-4 and IL-6 from Th2 cells increases synthesis of IgE [28]. Evidence for this is provided by *in vitro* data in which HIV-1 envelop glycoprotein (gp) 120, which acts as a viral superantigen, and gp160 and Tat proteins have shown to promote IL-4 induced IgE synthesis [28]. Moreover, HIV may induce synthesis of IL-6, resulting in polyclonal IgE production. Increased production of IL-6 has been suggested as a distinct mechanism affecting production of IgE [29]. Elevation of IgE may also be caused by production of antibodies specific for the virus itself [30]. Furthermore, it has been well documented that elevated IgE level amongst HIV infected adults is associated with more rapid progression of their disease as measured by declining CD4 cell count and poor prognoses [25,31]. It is also interesting to note the presence of cross-reactive T cells between HIV and *M. tuberculosis in vivo* which may contribute to the disease pathogenesis in coinfecting individuals [32].

In the present study, significantly higher IgE levels were observed in HIV seronegative TB patients coinfecting with intestinal helminthes compared to helminth negatives. This is due to the fact that, intestinal parasitic infections are potent stimulators of IL-4 dependent synthesis of both parasite specific IgE, which is important in the host immune response to parasites, and polyclonal IgE [33]. Parasite specific IgE attaches to high affinity Fc receptors on mast cells, and neighbouring specific immunoglobulin cross-link and trigger mast cell degranulation. This

process mediates an antiparasite response via the release of pro-inflammatory cytokines [34]. This mechanism has been suggested as the major cause of the elevated serum levels of IgE in tropical populations where the prevalence of parasites is very high [35]. We have previously shown that, intestinal parasitic infections cause immune activation by increasing memory CD4⁺ T cells as such availing more target cells which are reported to largely express CCR5 for easy infection by the non syncytium inducing HIV subtype C in Ethiopia [36]. Others have also reported that helminthic infections jeopardize the host's ability to generate protective immunity to HIV and *Mycobacterium tuberculosis* [5,6]. On contrary, the level of IgE in TB patients coinfecting with HIV was not significantly different in those with or without intestinal helminthes infection, though its level was higher in patients with helminthes. This might indicate the effect of HIV infection as potent stimulator of immune response and hence resulting in increased IgE synthesis irrespective of coinfection with intestinal worms.

Even though the number of patients included was very low, the present study pointed out a remarkable decline in serum IgE level after treatment for intestinal parasites. This is in line with the finding that elimination or reduction in intestinal worms following treatment resulted in a significant improvement in T cell proliferation and in gamma interferon production by peripheral blood mononuclear cells stimulated with PPD [37]. Moreover, vaccination with *Mycobacterium bovis* BCG (bacille Calmette-Guérin) significantly improved PPD specific immune responses in individuals treated with helminth drugs but not in those given placebo helminth treatment [37]. Decline in serum IgE after treatment for intestinal parasites was observed in children [38]. Interestingly, reversal of impaired cell-mediated immune response 3–6 months following chemotherapeutic cure of intestinal parasitic infections has also been reported [36,39]. These lend support to the present finding of reduced IgE after antiparasite chemotherapy, though it is difficult to ascribe the reduced IgE to only antiparasite chemotherapy in view of the fact that they were also treated for TB. Inclusion of patients with unsuccessful treatment of intestinal helminth infections may help to distinguish between the effects of TB chemotherapy and antiparasite treatment on IgE levels, in future studies.

Likewise, the significant decline in serum IgE levels after anti-TB chemotherapy observed in the present study is in line with a few earlier studies where significantly lower post treatment IgE concentration compared to its level before treatment were reported [15,40,41]. This may probably be associated with secretion of IL-12 by *M. tuberculosis* infected macrophages which in turn induces the development of Th1 cells that would secrete gamma IFN which might inhibit Th2 responses [42] and hence cause reduction of IgE. However, the decline in serum IgE level in HIV seropositive TB patients was not statistically significant, indicating the continued activation of the immune system by HIV [30]. On the other hand it is interesting to see the IgE levels in HIV positive patients with disseminated and extrapulmonary TB did not decline after therapy unlike the patients with pulmonary TB. This may probably indicate a heightened Th2 activation in the former cases compared to patients with pulmonary TB. Those patients with extrapulmonary TB whose IgE levels didn't decline after anti-TB chemotherapy might be patients with advanced HIV infection [43] reflecting association of the elevated IgE to advanced HIV disease [30].

Taken together, the results of this study indicated that, there was a remarkably elevated IgE response in TB patients with or

without HIV and/or intestinal helminthes infection before initiation of therapy. The IgE profile was significantly higher in patients coinfecting with HIV. The elevated profile significantly declined two months after anti-TB chemotherapy in HIV seronegative TB patients, but not in HIV seropositives. The decline may indicate a shift in immune response towards Th1 which is crucial for prognosis in TB patients. Further studies, following the patients until completion of anti-TB chemotherapy and also involving those patients who were not successfully treated for intestinal parasites, are recommended to fully understand the role of therapy.

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