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Early report

Decline in total serum IgE after treatment for tuberculosis

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Summary

Background Infection with *Mycobacterium tuberculosis* induces a type-1 immune response, whereas intestinal parasites elicit a type-2 response. Given that type-1 and type-2 responses inhibit each other, we investigated if *M tuberculosis* downregulates serum IgE, a marker of a type-2 response.

Methods A prospective study was done in the Western Cape Province of South Africa, where tuberculosis and intestinal-parasite infection are common. Total serum IgE was determined for 37 controls and for 33 adolescent patients at presentation with tuberculosis and after successful completion of treatment. IgE specific for ascaris and allergens were measured in a subset of these individuals. Mantoux skin tests were done on 35 controls and on 31 patients at diagnosis.

Findings Total IgE concentrations were high in controls (mean 313 kU/L) and in patients before treatment (mean 457 kU/L, $p=0.085$) and declined in all patients following successful treatment (mean 175 kU/L, $p<0.0001$). Post-treatment IgE concentrations did not differ from concentrations in controls. Ascaris-specific IgE was lower in controls (mean 1.73 kU/L) than in patients before treatment (4.62 kU/L, $p=0.023$) and was 2.39 kU/L in patients after treatment ($p=0.0625$). Tuberculin induration correlated inversely with IgE in patients but not in controls.

Interpretation Infection with *M tuberculosis* as such is not incompatible with a prominent IgE response. IgE concentrations decreased after successful treatment of tuberculosis, showing that IgE concentrations in human beings can be downregulated under these circumstances, presumably due to enhancement of a type-1 response.

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Introduction

It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis* and that about 90% of infected individuals do not develop clinical disease.¹ The outcome after infection with *M tuberculosis* is determined by cell-mediated immunity. Macrophages infected with *M tuberculosis* secrete interleukin 12, which induces the development of type-1 lymphocytes secreting interleukin 2 and interferon γ .² Interferon γ , in turn, activates macrophages and enhances their microbicidal activity.

The importance of an appropriate type-1 response for the successful elimination of mycobacterial infections is highlighted by recent reports of uncontrolled mycobacterial infection in patients with defective interferon γ or interleukin 12 receptors.^{3–6} A type-2 response, on the other hand, is characterised by the secretion of interleukins 4, 5, 6, 10, and 13 and by the production of non-opsonic antibodies including IgG4 and IgE. Such a response is usually elicited by helminthic infections or an atopic predisposition.² Type-1 and type-2 cells negatively cross regulate each other in vitro and in experimental animals: interferon γ inhibits a type-2 response, while interleukin 4 inhibits a type-1 response.²

Delayed-type hypersensitivity reactions such as tuberculin skin tests reflect a type-1 response whereas IgE production reflects a type-2 response. Several recent studies indicate that mycobacterial or viral infection may reduce IgE levels or suppress atopy or both.⁷ Japanese schoolchildren who were Mantoux-skin-test positive had lower IgE concentrations and type-2 cytokines than tuberculin-negative individuals⁸ and natural measles infection reduces the incidence of atopy to half of that seen in vaccinated children.⁹ In mice allergic to ovalbumin, treatment with killed *M vaccae* inhibits IgE and interleukin 5 responses,¹⁰ and infection with *M bovis* BCG suppresses ovalbumin-induced airway eosinophilia.¹¹ These studies suggest that a type-2 response can be suppressed by a type-1 response in vivo. We hypothesised that *M tuberculosis*-infected individuals, who successfully contained the organism and did not develop disease, would have a prominent type-1 response and low IgE concentrations, whereas patients presenting with tuberculosis would have a less efficient type-1 response and higher IgE concentrations. Furthermore, given that successful outcome after infection with *M tuberculosis* is driven by a type-1 response, we hypothesised that successful treatment for tuberculosis would downregulate type-2 responses.

Methods

This study was done in the Western Cape Province of South Africa, where the incidence of tuberculosis was 682/100 000 in 1995¹² and where infestation with intestinal parasites, especially *Ascaris lumbricoides* and *Trichuris trichiura*, is common.¹³

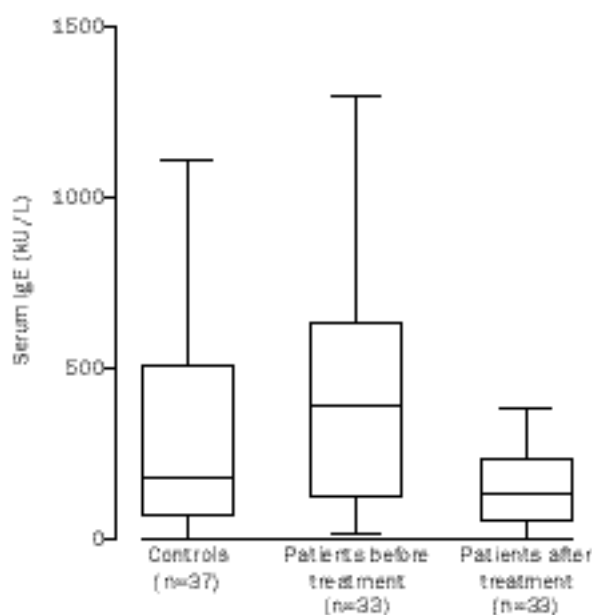


Figure 1: Serum IgE concentrations in controls, patients before treatment, and patients after treatment for tuberculosis

Median IgE (171 kU/L, 394 kU/L, and 129 kU/L, in controls, patients before treatment, and patients after treatment, respectively) are indicated with horizontal bars. The vertical bars indicate the range and the horizontal boundaries of the boxes represent the first and third quartiles.

Adolescents were studied, because the incidence of tuberculosis between the ages of 5 and 12 years is low,¹⁴ because the diagnosis of tuberculosis in adolescence (and adulthood) is more accurate than in childhood,¹⁵ and because IgE concentrations vary less than in early childhood.^{16,17} Between 1995 and 1998, 50 adolescents with tuberculosis were referred to us from socioeconomically poor suburbs in the Cape Town metropolitan area, where BCG is routinely administered in the neonatal period and where BCG coverage is over 98%. Controls were recruited by asking each patient to bring along a friend from the same peer and age group. Controls were randomly taken from this group. Of the 50 patients, four were excluded from the study because they did not complete their therapy, and 13 were not analysed because serum was not collected for IgE determination at diagnosis and after therapy. The final sample consisted of 33 patients (19 females, 14 males, mean age 15.1 [SD 2.3] years) and 37 controls (18 females, 19 males, mean age 15.2 [1.9] years). All patients had clinical features consistent with tuberculosis, supported by typical chest radiograph findings or positive cultures for *M. tuberculosis* or both. Chest radiography findings included cavities in the upper lobes (20 cases), hilar lymphadenopathy (two cases), pleural effusions (seven cases),

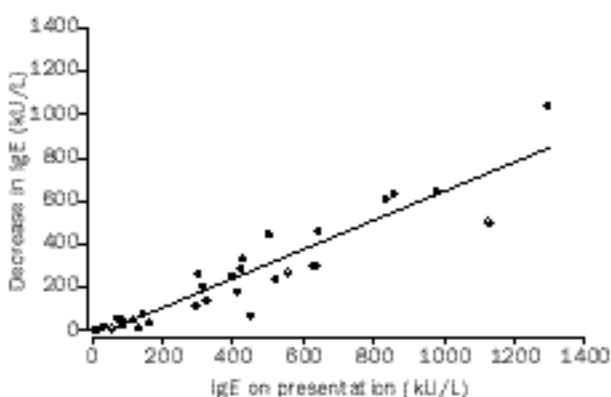


Figure 2: Correlation of serum IgE concentrations of patients on presentation with the decrease in serum IgE concentrations following treatment of tuberculosis

and four smear or culture-positive cases where we could not classify the chest radiography findings in any of these categories. A Mantoux skin test (0.1 mL [5TU] Japanese freeze-dried tuberculin, induration measured after 48–72 h) was done on 31 patients and 35 controls. All patients included in the study were successfully treated with directly observed short-course combination chemotherapy. Venous blood was taken from control individuals and from patients before initiation of treatment and after successful completion of treatment (mean follow-up time 9.8 [1.24] months, after initiation of treatment). We did not do a Mantoux skin test on the patients after treatment.

Total serum IgE concentrations were measured with a radioimmune assay (Pharmacia, Uppsala, Sweden). On a random selection of sera (which included 23 patients and 33 controls) specific IgE against *A. lumbricoides*, house dust mite, cockroach, and Bermuda grass was measured using ImmunoCAP radio-allergo-sorbent (CAP RAST) tests (Pharmacia, Uppsala, Sweden). HIV-1 and HIV-2 infection was excluded in all patients with a microparticle enzyme immunoassay (AxSYM, Abbott, Wiesbaden-Delkenheim, Germany). All the patients or legal guardians gave their written informed consent and had HIV-test counselling. The study was approved by the ethics committee of the University of Stellenbosch.

Non-parametric statistical tests were used and computed with the help of the SPSS programme. Analyses were done with the Wilcoxon signed-rank test, the Mann-Whitney test for comparison of independent groups, and the Spearman rank test for correlations. The Fisher exact test was used to compare specific IgE concentrations between controls and tuberculosis patients. The McNemar exact test was used to compare IgE concentrations before and after treatment of patients. Individuals with measurable specific serum IgE concentrations (>0.3 kU/mL) were considered to be responders and individuals with concentrations below 0.3 kU/L were considered to be non-responders. Level of significance was set at the 95% cut-off point.

Results

The mean serum IgE concentration was 313 kU/L (SD 352, median 171 kU/L) in controls and 457 kU/L (SD 455, median 394 kU/L) in patients before treatment ($p=0.085$, figure 1). Mean IgE concentrations in patients after treatment was 175 kU/L (SD 173, median 129 kU/L). The post-treatment concentrations did not differ significantly from concentrations in controls. In patients the difference in IgE concentration before and after treatment was highly significant ($p<0.0001$); in every patient the IgE concentration was higher before than after treatment. The decrease in IgE correlated with the concentration of IgE on presentation ($r=0.93$, $p<0.001$, figure 2).

Mean ascaris-specific IgE was significantly lower in controls (1.73 kU/L, SD 3.94, median 0.30 kU/L) compared with patients before treatment (4.62 kU/L, SD 10.89, median 1.10 kU/L; $p=0.023$). Mean ascaris-specific IgE in patients following treatment was 2.39 kU/L (SD 5.71, median 0.40 kU/L; $p=0.0625$). The specific IgE concentrations for cockroach, house dust mite, and Bermuda grass were not significantly different between controls and patients before and after treatment.

Eight controls and two patients did not have any Mantoux skin test induration. After excluding individuals who showed no induration after Mantoux testing, the mean induration of controls (19.05 mm, SD 6.52) did not differ from that of patients before treatment (21.8 mm, SD 5.69). The size of Mantoux induration correlated inversely with serum IgE ($r=-0.406$, $p=0.023$)

in patients, but not in controls ($r=-0.233$, $p=0.178$). There was no statistical difference between these two correlation coefficients (Fisher z test).

Discussion

This study was done in a community with a high incidence of tuberculosis¹⁸ and a high infestation rate with the parasites *A lumbricoides* and *T trichiura*,¹³ a situation that is common in many developing countries. Most control individuals (28 of 36 tested) had Mantoux test indurations over 15 mm and the distribution of skin-test responses was similar to that of patients, indicating that most controls had been exposed to *M tuberculosis*.^{19,20} Mean total serum IgE concentrations in both the controls and patients presenting with tuberculosis were higher than the normal range for individuals living in better socioeconomic circumstances. This may reflect the high level of intestinal parasite infestation in the study community. At presentation with tuberculosis, patients had higher total IgE concentrations than controls, but the difference was not statistically significant. Therefore, the present study does not support our hypothesis that healthy individuals infected with *M tuberculosis* have lower type-2 responses than patients with tuberculosis. One group, however, previously reported lower IgE concentrations in health workers exposed to *M tuberculosis* than in a large cohort of Indonesian patients presenting with tuberculosis.²¹

The key finding from this study is a pronounced and consistent decline in IgE concentrations in patients after successful treatment for tuberculosis. Trivial reasons for the striking decrease in total IgE concentrations in tuberculosis patients are unlikely. First, reduction in IgE concentrations by antituberculosis drugs has not been documented. On the contrary, rifampicin binds to and activates the glucocorticoid receptor²² and there is mounting evidence that glucocorticoids can enhance type-2 rather than type-1 responses.²³ Second, reduction in the parasite burden, which could decrease IgE concentrations, has not been described for antituberculosis drugs. Third, we could not document that any of the patients received anthelmintics during their tuberculosis treatment. Serum IgE was not repeated 9 months later in the control individuals, but IgE concentrations in worm-infested populations rapidly increase during childhood and thereafter stabilise in early adulthood, or gradually decline over many years.^{16,17} Significant changes in the IgE concentrations of the control individuals are therefore highly unlikely. Taken together, the decline in IgE concentrations in patients after successful treatment of tuberculosis supports the hypothesis that successful treatment of tuberculosis is associated with downregulation of type-2 responses. Previous publications that documented the reversal of skin-test anergy²⁴ and an increase in T-cell responses²⁵ support the concept of enhanced type-1 responses after chemotherapy of tuberculosis.

We did not examine stool specimens to quantify the rates and severity of parasite infestation in our patients, but more patients with tuberculosis had ascaris-specific IgE antibodies than controls. Parasite infestation and tuberculosis are both associated with poverty and social deprivation.^{26,27} In this study, controls and patients were from the same communities and the increased frequency of ascaris-specific antibodies in patients raises the question of whether infestation with *A lumbricoides*

contributes to susceptibility to tuberculosis. It is noteworthy that *A suum* impairs T-cell function in mice²⁸ and that ascaris spends a stage of its lifecycle in the lungs, where it may induce a local type-2 immune response. Studies in mice²⁹⁻³¹ and human beings^{32,33} indicate that parasite-induced type-2 dominance may suppress cell-mediated immunity. Bentwich and colleagues hypothesised that intestinal parasites exacerbate the course of HIV infection,³⁴ which like tuberculosis is controlled by cell-mediated immunity. In 1994, Bundy and colleagues calculated that 28% of the world's population is infected with ascaris and 25% with *T trichiura*, causing substantial morbidity.³⁵ If intestinal helminths indeed exacerbate HIV disease or tuberculosis, their burden on global morbidity may be even higher.

The inverse correlation between IgE concentrations and Mantoux size in patients may be due to cross regulation of type-1 and type-2 responses. In this study, the apparent lack of a similar correlation in controls may be due to the small size of the cohort studied. Shirakawa and colleagues found lower IgE concentrations in a large cohort of Japanese schoolchildren who were tuberculin-skin-test positive and reasoned that mycobacterial infection may reduce type-2 response including atopy.⁸

In conclusion, this study and others^{7,8,10,11} suggest that the immune response to *M tuberculosis* and to nonpathogenic mycobacteria suppresses a type-2 response, which plays a key role in the induction and maintenance of high IgE concentrations in parasite infestation and in disorders such as atopy.

Contributors

J F A Adams, E H Scholvinck, R P Gie, P C Potter, N Beyers, and A D Beyers contributed to the conception of the study and to writing the paper. J F A Adams, E H Scholvinck, and A D Beyers obtained and analysed data. R P Gie, and N Beyers recruited patients and obtained data.

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