IgE, Matrix Metalloproteinases, and Tuberculosis: Immunologic Consequences of Helminth Co-Infection

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Artificial Intelligence Disclaimer: Chat GPT was used to check and annotate R-code and to check text for spelling and grammar. It was not used to generate data (text/code etc) de novo.

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To the Editor:

Introduction

Tuberculosis (TB) and soil-transmitted helminth (STH) co-infections are common in tropical regions and may adversely affect TB outcomes(1, 2). Helminths can impair TB-specific immunity and have long-lived immunological effects(3, 4). Matrix metalloproteinases (MMPs), which mediate extracellular matrix degradation and lung tissue destruction in TB, are elevated in TB–STH coinfected individuals(1, 2, 5). STHs are potent inducers of IgE, which is implicated in MMP regulation and pulmonary damage in chronic lung diseases(6). However, whether helminth-induced IgE contributes to MMP-driven tissue destruction in TB remains unknown.

In our previous analysis of a TB patient cohort from Peru, we reported elevated MMP concentrations in TB–STH coinfected individuals, associated with increased radiographic severity(1). In this study, we examined STH polyparasitism, plasma IgE, and MMP concentrations to investigate whether IgE might be a key immunological link between helminth infection and TB-associated lung pathology.

Methods

We conducted a case-control study in Iquitos, Peru, recruiting newly diagnosed, smear- or culture-confirmed pulmonary TB patients and age-/sex-matched community controls(1). Blood was taken for plasma analysis by ELISA and Luminex bead array of MMPs, TIMP-1, IgE, and *Strongyloides* antibodies; sputum for TB confirmation and stool for copro-parasitology. When available, routine TB chest radiographs (CXRs) were independently scored by 2 blinded reviewers using the TIMIKA system to assess lung damage(7). Participants were classified into four groups: TB+STH+, TB+STH-, TB-STH+, TB-STH-. We conducted non-parametric

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tests and multivariable linear regression on log-transformed IgE and MMP/TIMP-1 concentrations. Ethical approval was granted by National Health Institute of Peru, Regional Health Directorate, and participating hospitals. All participants provided informed consent prior to enrolment.

Results

Sixty-one TB-positive and 51 TB-negative participants were recruited. Groups were comparable in age, sex, education, smoking, alcohol and substance use, and socio-economic status. Diagnosed STHs included *Strongyloides stercoralis*, *Trichuris trichiura*, hookworm, and *Ascaris lumbricoides*, with *Strongyloides* (p=0.05) and hookworm (p=0.01) independently significantly prevalent in TB-positive individuals. The adjusted odds ratio for TB positivity increased with the number of STH species detected: 2.69 (95%CI 1.14–6.59) for ≥1 species, 3.62 (95%CI 1.31–11.34) for ≥2 species, and 4.71 (95%CI 1.01–34.45) for ≥3 species, adjusting for age, sex and poverty index.

Plasma IgE was significantly higher in STH-positive participants, regardless of TB status (Figure 1A): median 2,196 ng/mL in TB+STH− versus 11,923 ng/mL in TB+STH+ (p<0.0001). Participants with eosinophilia (>6%) had non-significantly increased median IgE levels compared to those with low/normal counts (13,351 ng/mL [IQR: 9,107] vs. 6,017 ng/mL [IQR: 9,881], p=0.21). Among STH-positive individuals, IgE increased with polyparasitism (Figure 1B). Controlling for TB and polyparasitism, all STHs were positively associated with IgE: *Strongyloides* > hookworm > *Trichuris* > *Ascaris* (Figure 1C). This association was significant for *Strongyloides* (beta 3.23, 95% CI 2.00–5.21, p<0.001)). Adjusting for TB, individuals with one STH species had 3.14-fold higher IgE (p<0.001), and those with over 2

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species had 4.72-fold higher IgE (p<0.001), than STH-negative participants (Figure 1D). TB positivity was not associated with increased IgE.

To investigate whether IgE may contribute to TB-associated lung tissue destruction, we measured plasma MMPs and TIMP-1 (tissue inhibitor of MMP-1) concentrations. Although there was group and individual variability, overall TB−STH− participants had the lowest MMP, IgE and highest TIMP-1 concentrations, while TB+STH+ had the opposite with highest MMP and IgE and lowest TIMP-1 concentrations (Figure 2A). All MMPs measured including MMP-1, -8, and -9 correlated positively with IgE concentrations and were generally higher in TB-positive patients (Figure 2B). In contrast, TIMP-1 correlated negatively with IgE and was lower in TB-positive individuals. Linear regression controlling for STH-positivity showed TB was associated with all MMPs and negatively with TIMP-1 (e.g., MMP-8: beta 3.87, 95% CI 2.80–5.34, p<0.001). However, when controlling for TB, IgE was also significantly positively associated with all MMPs. The strongest associations were MMP-8 (beta 1.23, 95% CI 1.09–1.38, p<0.001) and MMP-9 (beta 1.21, 95% CI 1.07–1.37, p<0.01), corresponding to 23% and 21% increases in MMP concentration per 1-unit increase in IgE. TIMP-1 showed a non-significant negative association (beta 0.96, 95% CI 0.91–1.01, p=0.08). A positive, but non-significant correlation was seen between IgE concentration and CXR score.

Discussion

This study identifies helminth-associated IgE elevation as a potential immunological driver of MMP-mediated tissue damage in pulmonary TB. STH infection, particularly polyparasitism, was independently associated with elevated plasma IgE concentrations and increased odds of active TB. IgE levels were positively

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associated with MMP-1, -8, -9, -10 and -13, while inversely associated with TIMP-1, independent of TB status. These findings indicate that helminth-induced immune responses may amplify matrix-degradation in TB.

Although TB infection showed the strongest association with MMP upregulation, IgE demonstrated an independent, dose-responsive relationship with MMP concentrations. This supports a model where STH-associated IgE contributes to lung matrix breakdown, potentially worsening TB-related pathology. We previously reported an association between elevated MMPs and lung damage(1). In this analysis, IgE concentrations were positively but not significantly associated with radiographic severity, likely due to limited power.

IgE is central to type 2 immunity and implicated in pulmonary damage in asthma, COPD, and hyper-IgE syndromes, where it correlates with airway inflammation, increased MMP activity, and impaired lung function(8, 9). Our findings extend this paradigm to TB, with IgE-driven immune activation worsening disease via extracellular matrix degradation. Although strongly associated with helminths, IgE was not significantly associated with TB, supporting the view that in helminth-endemic settings, IgE elevation reflects parasitic not TB-specific responses(10).

The association between STH polyparasitism and TB risk supports the hypothesis that helminth infections impair protective antimycobacterial immunity(3, 4). Cumulative immune dysregulation in poly-parasitised individuals may increase TB susceptibility and immunopathology(4). The relationship between STHs and IgE varied by species, with *Strongyloides* showing the strongest association, possibly due to its recurrent tissue-invasive life cycle.

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This study has limitations. Its cross-sectional design precludes causal inference, and *Strongyloides* serology may overestimate active infection. However, the consistency of associations across STH species and immune markers, along with adjustment for demographic and socioeconomic variables, supports the robustness of our findings.

In summary, we identify IgE as a potential mechanistic link between helminth co-infection and enhanced MMP activity in pulmonary TB. These findings have implications for TB-endemic settings with high helminth prevalence, where integrated deworming may mitigate TB-associated tissue damage and improve clinical outcomes.

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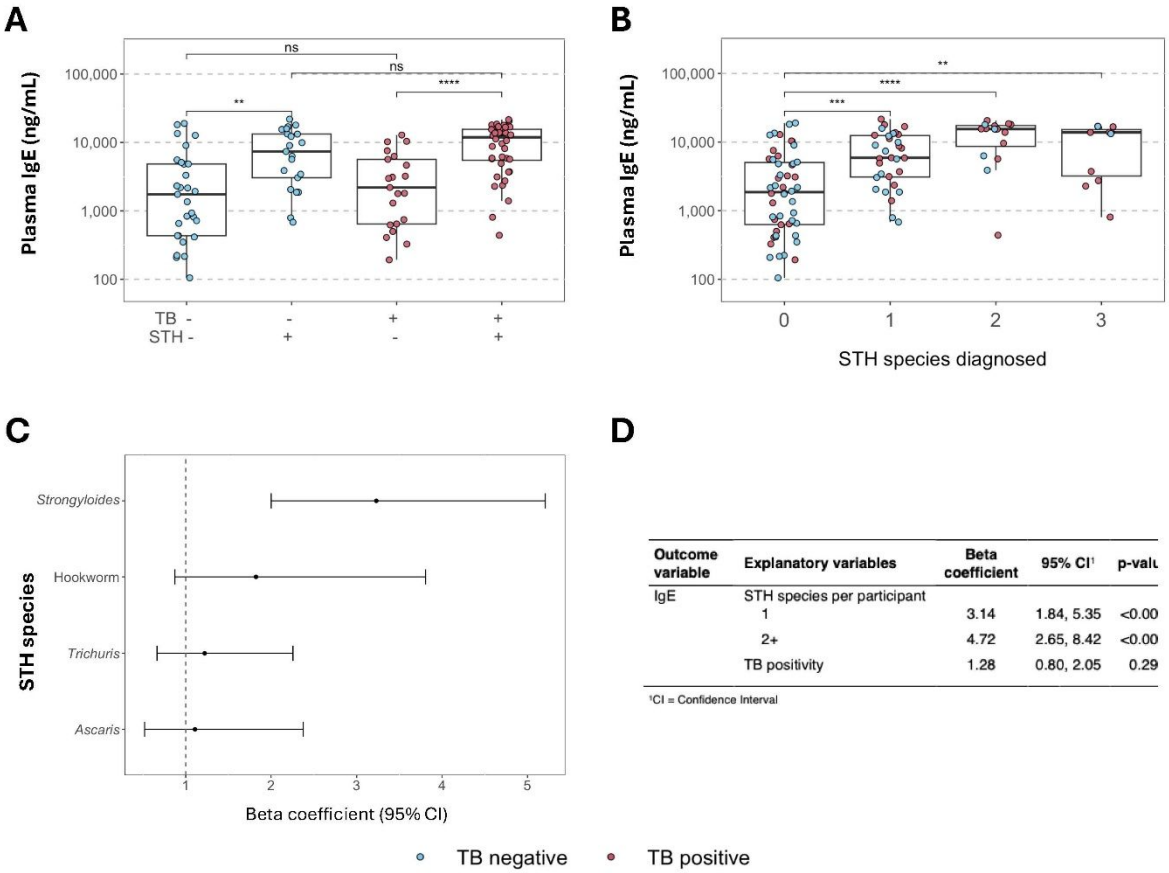
Figures



Outcome variable	Explanatory variables	Beta coefficient	95% CI[1]	p-valu
IgE	STH species per participant			
	1	3.14	1.84, 5.35	<0.00
	2+	4.72	2.65, 8.42	<0.00
	TB positivity	1.28	0.80, 2.05	0.29

[1]CI = Confidence Interval

Figure 1. Relationship between plasma IgE, STH infection, and TB status

A. *Plasma IgE concentrations stratified by TB and STH infection status.* ***B.*** *IgE concentrations by number of STH species per participant (polyparasitism). In A and B, each circle represents a participant (blue = TB−, red = TB+). IgE values are plotted on a* $\log_{10}$ *scale. Boxes show median and interquartile range (IQR); whiskers extend to 1.5× IQR. Statistical testing: Wilcoxon rank-sum.* ***C.*** *Forest plot of exponentiated beta coefficients from linear regression with* $\log_{10}$ *IgE as the outcome. Each STH species included as a binary predictor, adjusted for TB status. Coefficients reflect fold-change in IgE (e.g. Strongyloides associated with 3.23-fold higher IgE [95% CI: 2.00–5.21,* $p < 0.001$*]).* ***D.*** *Linear regression of IgE by degree of STH polyparasitism, adjusted for TB status. Coefficients show fold-change in IgE compared to STH-negative participants (e.g. ≥2 species: 4.72-fold increase).*

Abbreviations: TB = tuberculosis; STH = soil-transmitted helminth; CI = confidence interval.

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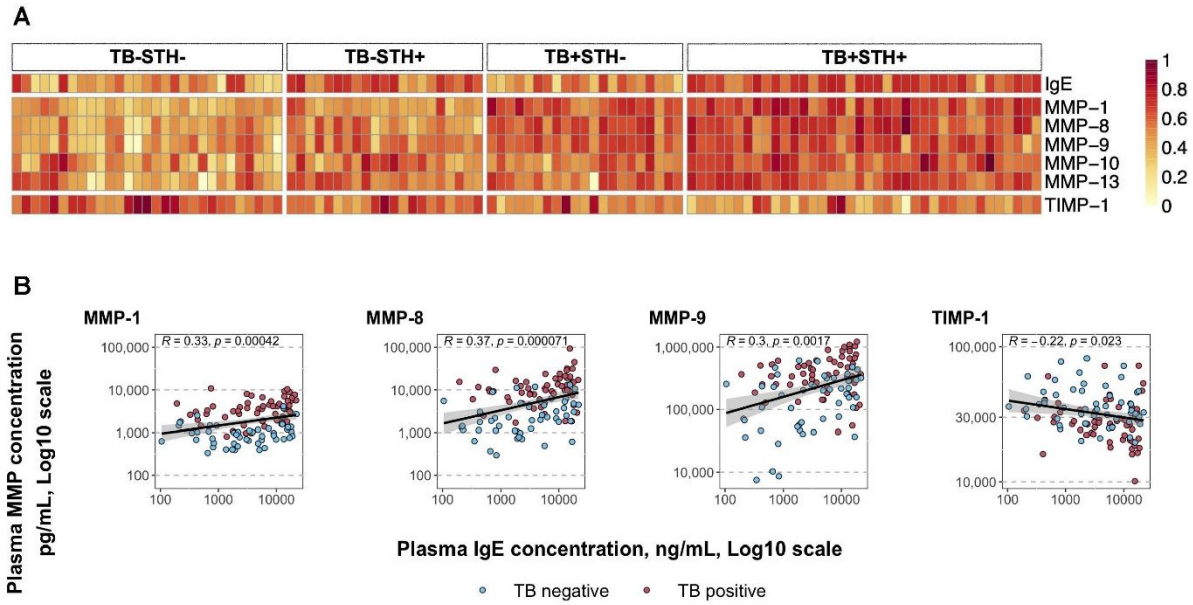

Figure 2. Relationship between plasma IgE and MMP concentration

Figure 2A*: Heatmap showing individual level data of IgE, MMP and TIMP-1 concentrations from the four participant groups, each cell represents one participant. All data were log-adjusted to normalise the data, then scaled across analytes to allow for cross-analyte comparison.*

Figure 2B: *Scatterplot of plasma IgE concentrations plotted against MMP & TIMP-1 concentrations, for TB-negative (blue) and TB-positive (red) individuals. Each circle represents a single individual, and the regression line indicates the relationship between IgE and MMP-1. Data are displayed on a Log10 scale for normalisation of non-parametric data. The correlation coefficient (R) represents the strength and direction of the association, and statistical significance was assessed using Spearman's rank correlation test.*

Abbreviations: TB = tuberculosis; STH = soil-transmitted helminth; TB-STH- TB-negative, STH-negative; TB-STH+ TB-negative, STH-positive; TB+STH- TB-positive, STH-negative and TB+STH+ TB-positive, STH-positive participants.

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