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Immunomodulatory effects of *Strongyloides stercoralis* infection in patients with allergic diseases: A clinical analytical study

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Abstract
Background: The immunomodulatory effect of helminths, such as *Strongyloides stercoralis* has indicated a possible protective effect in the increasing prevalence of allergic diseases.
Aim: The aim of the study was to assess the effects of *S. stercoralis* infection on the immune system of allergic patients.
Methodology: A clinical analytical study was conducted in Basrah, Iraq, involving a total of 120 participants who were categorized as healthy control, allergic, and allergic and co-infected with *S. stercoralis*. ELISA and flow cytometry were used to determine immunological markers (IL-10, TGF-β, IL-4, IL-5) and regulatory T cells (Tregs).
Results: Co-infected individuals showed a considerable increase in CD4+CD25+FoxP3+ Tregs (7.80% ± 1.08% vs. 3.30% ± 0.66, P = 0.001) in comparison to allergic individuals alone. This was accompanied by a dramatic elevation in anti-inflammatory cytokines IL-10 (44.90 ± 7.90 vs 12.35 ± 4.10 pg/mL, P < 0.001) and TGF-β (342.59 ± 57.76 vs 177.70 ± 40.62 pg/mL, P < 0.001). Conversely, Th2-associated cytokines IL-4 and IL-5 showed significant suppression in the presence of *S. stercoralis* (16.91 ± 4.49 vs 24.38 ± 4.97 pg/mL and 15.27 ± 3.15 vs 23.18 ± 3.98 pg/mL, respectively, P < 0.01). The highest levels of total serum IgE occurred in the co-infected group (1213.92 ± 249.40 IU/mL) indicating a polyclonal response which is paradoxically accompanied by regulatory inhibition. There was a significant positive relationship between Treg expansion and the IL-10 levels (r = 0.78, P < 0.001).
Conclusion: *S. stercoralis* infection triggers a robust regulatory circuitry which efficiently regulates Th2-mediated allergic inflammation, which is why it has potential as a source of new immunotherapeutic approaches.

Keywords: *S. stercoralis*, IL-10, TGF-β, IL-4, IL-5

Introduction

Helminthic parasitic diseases are a major health concern worldwide as they impact hundreds of millions of people, especially in tropical and subtropical areas [1]. *Strongyloides stercoralis* is one of such parasite capable of establishing chronic infections in a human host and may last decades because it has an autoinfective life cycle [2]. The resulting disease known as strongyloidiasis, is typically asymptomatic or mild and non-specific, making it hard to detect and be spread without symptoms [3]. But in immunocompromised patients, the infection may develop into a life threatening hyperinfection syndrome [4].

Conversely, the prevalence of allergic diseases, including asthma, allergic rhinitis, and eczema, is significantly increasing across the globe with a significant health and economic impact [5]. These types of disorders are defined by excessive immune system response to otherwise harmless allergens, which is usually driven by type 2 immune responses (Th2) that require the release of immunoglobulin E (IgE) and the release of mast cells and eosinophils [6]. This observation has led to the formulation of the so-called hygiene hypothesis, where a lack of exposure to microbes and parasitic infections in contemporary surroundings could be the cause of the increasing prevalence of allergic illnesses and autoimmune disorders [7].

The intricate interaction between parasitic infections and the host immune system has captured much attention over the past few years, especially with regard to the immunomodulatory nature such parasites can have on the progression of allergic diseases [8]. Helminths have been known to adjust host immune responses via complex interactions, enabling them to survive and avoid immune clearance [9]. They involve the activation of regulatory T cells (Tregs) and the secretion of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which have the potential to inhibit the overabundance of immune responses, including those related to allergy [10].

Within the framework of strongyloidiasis, it has been reported that the *S. stercoralis* infection might result in a mixed-immune response, comprising both Th2-type (associated with allergy) and regulatory elements [11]. As an example, the high levels of total and parasite-specific IgE levels in strongyloidiasis patients have been observed, which are in line with the allergic responses [12]. Nevertheless, increasing evidence is emerging to indicate that *S. stercoralis* can also have protective immunomodulatory properties towards allergic diseases [13]. These actions have been postulated to be mediated through mechanisms like induction of regulatory T cells which secrete IL-10 and TGF-β hence dampening allergic inflammatory reactions [14].

The relationship between *S. stercoralis* infection and allergic diseases is complex and often yields contradictory findings. Although there is evidence of parasitism infection potentially lowering the threat or intensity of allergies, other studies report no apparent consequences or even an increase of allergic symptoms in some circumstances [15]. All these discrepancies can be explained by various factors such as the intensity of infections, duration of exposure, the genetic

background of the host, the presence of other parasites during exposure and the differences in research methods.

Although there has been a rising body of research in this area, there is a dearth of analytical clinical studies that specifically examine the immunomodulatory impact of *S. stercoralis* infection on patients who have allergic diseases in a particular clinical situation. Elucidation of these intricate immune interactions is essential to designing new therapeutic and preventive interventions to allergic diseases and, perhaps, to consider the application of particular parasitic parts as immunotherapeutic agents. The aim of this clinical analytical study is to determine the impact of *Strongyloides stercoralis* infection on patients with allergic diseases regarding immunomodulatory effects through the evaluation of changes in the main immunological markers like cytokines (IL-10, TGF-β, IL-4, IL-5, IFN-γ), counts of regulatory T cell (Tregs) and the total and allergen-specific The comparison of these indicators between patients with strongyloidiasis and allergic diseases, patients with allergic diseases alone, and healthy individuals will help to identify the possible role of *S. stercoralis* infection in regulating the allergic immune response.

Methodology

Study Setting

The current clinical analytical research was carried out in Basrah, Iraq, and targeted the local population visiting special clinics of allergy and internal medicine. The study aimed to investigate the immunomodulatory interactions between *Strongyloides stercoralis* infection and allergic signs.

Inclusion Criteria

This study had an inclusion criteria of (18-65) years old. The inclusion criteria was a definite clinical diagnosis of conditions like bronchial asthma, allergic rhinitis or chronic urticaria, defined by specialist physicians through standardized diagnostic systems. Inclusion of the infected groups required the laboratory diagnosis of *S. stercoralis* by various parasitological tests to be diagnostic.

Exclusion Criteria

The elimination of possible confounding factors was carried out through the strict application of the exclusion criteria. Patients who are also infected by other soil-transmitted helminths were not included in order to avoid immunological cross-reactivity. Moreover, ineligible were patients who had taken systemic corticosteroids, immunosuppressive therapy, or anthelmintic drugs in the three months before the study. Other exclusion criteria were chronic systemic or autoimmune conditions, pregnancy or lactation.

Parasitological Diagnostic Procedures

Parasitological diagnosis was performed following a strict protocol to provide great sensitivity. Each participant was sampled using fresh stool in sterile containers. Larval screening and concentration was done through the formol-ether concentration method that entails the emulsification of the stool in 10% formalin and centrifugation with diethyl ether [16]. In order to further improve the detection, the Haroda-Mori filter paper culture technique was used, which used the natural water tropism of the larvae to isolate them [17].

Immunological Assays

To perform an immunological analysis, each participant had about 5 mL of peripheral venous blood gathered. Anti-inflammatory cytokines (IL-10 and TGF-β) and Th2-related cytokines (IL-4, IL-5, and IFN-γ) were quantitatively determined using the high sensitivity Enzyme-Linked Immunosorbent Assay (ELISA) kits according to the specifications of the manufacturer [18]. An electrochemiluminescense immunoassay (ECLIA) on auto platform was used to measure total serum Immunoglobulin E (IgE) levels [10].

Flow Cytometry

Multi-color flow cytometry was used to characterize the regulatory T cells (Tregs). Peripheral blood mononuclear cells (PBMCs) were then isolated and stained with fluorochrome-conjugated monoclonal antibodies against CD4, CD25 and intracellularly stained with transcription factor FoxP3, the ultimate Treg lineage marker [8].

Statistical Analysis

The statistical analysis was done in SPSS (Version 26.0). All the continuous variables were calculated using descriptive statistics. The ANOVA test was employed to compare differences between the three study groups and then Tukey was used to compare the differences. The correlation coefficient developed by Pearson was used to investigate the interrelations between level of cytokines and Treg percentages. The statistical significance was taken to mean a P-value of less than 0.05.

Results

Clinical and immunological analysis of the three study groups showed that there was a significant difference in the expression of the regulatory markers and Th2-related cytokines. The subsequent sections present the results of the comparisons between Healthy Controls (HC), Allergic Patients (AP), and Allergic Patients co-infected with *Strongyloides stercoralis* (AP+SS).

Demographics and Parasitological Results

In this study, 120 participants were used in an equal number of three groups (n=40 each group). All the patients in the AP+SS group were reported to have *S. stercoralis* larvae by the formol-ether concentration and Harada-Mori culture. The prevalence of the allergic conditions in the sample population was bronchial asthma (45%), allergic rhinitis (35%), and chronic urticaria (20%), and there was no significant difference between the distribution of allergic conditions in AP and AP+SS groups.

Immunological Markers/Cytokine Profiles

The researchers discovered a specific change in the cytokine profile of allergic patients with *S. stercoralis* co-infection. The anti-inflammatory cytokine levels were higher in AP+SS group than in AP group and Healthy Controls (Table 1).

Table 1: Comparison of cytokine levels and immunological markers across study groups

Marker	Healthy Controls (n=40)	Allergic Patients (n=40)	Allergic + *S. stercoralis* (n=40)	p-value
IL-10 (pg/mL)	14.90 ± 3.25	12.35 ± 4.10	44.90 ± 7.90	< 0.001
TGF-β (pg/mL)	193.93 ± 26.92	177.70 ± 40.62	342.59 ± 57.76	< 0.001
IL-4 (pg/mL)	4.99 ± 0.98	24.38 ± 4.97	16.91 ± 4.49	< 0.001
IL-5 (pg/mL)	4.02 ± 1.01	23.18 ± 3.98	15.27 ± 3.15	< 0.001
IFN-γ (pg/mL)	31.17 ± 5.04	27.41 ± 6.42	25.11 ± 4.24	0.062
Tregs (%)	3.66 ± 0.47	3.30 ± 0.66	7.80 ± 1.08	< 0.001
Total IgE (IU/mL)	84.78 ± 21.17	642.33 ± 167.25	1213.92 ± 249.40	< 0.001

Note: Data are presented as Mean ± SD. P-values were calculated using one-way ANOVA.

Increase of Regulatory T cells (Tregs) and Anti-inflammatory Cytokines

The proportion of CD4+CD25+FoxP3+ regulatory T cells dramatically increased in patients with strongyloidiasis (7.80% ± 1.08%) over controls with allergies without the infection (3.30% ± 0.66%, P < 0.001). This growth was highly associated with increased IL-10 and TGF-β (Figure 1).

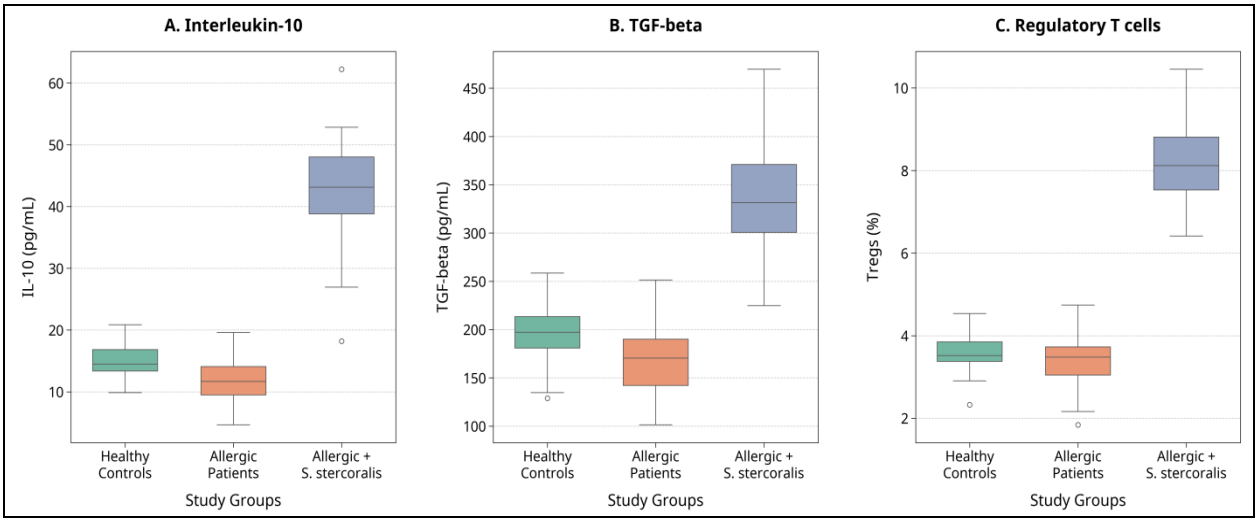

Fig 1: Comparison of regulatory markers across study groups. (A) interleukin-10 levels, (B) TGF-β levels, and (C) percentage of CD4+CD25+FoxP3+ Tregs

Modulation of Th2 Responses and IgE Levels

Although the total IgE levels were the highest in the AP+SS group (1213.92 ± 249.40 IU/mL), the Th2-related cytokines IL-4 and IL-5 were significantly less in the co-infected group compared with the allergic-only group (Figure 2).

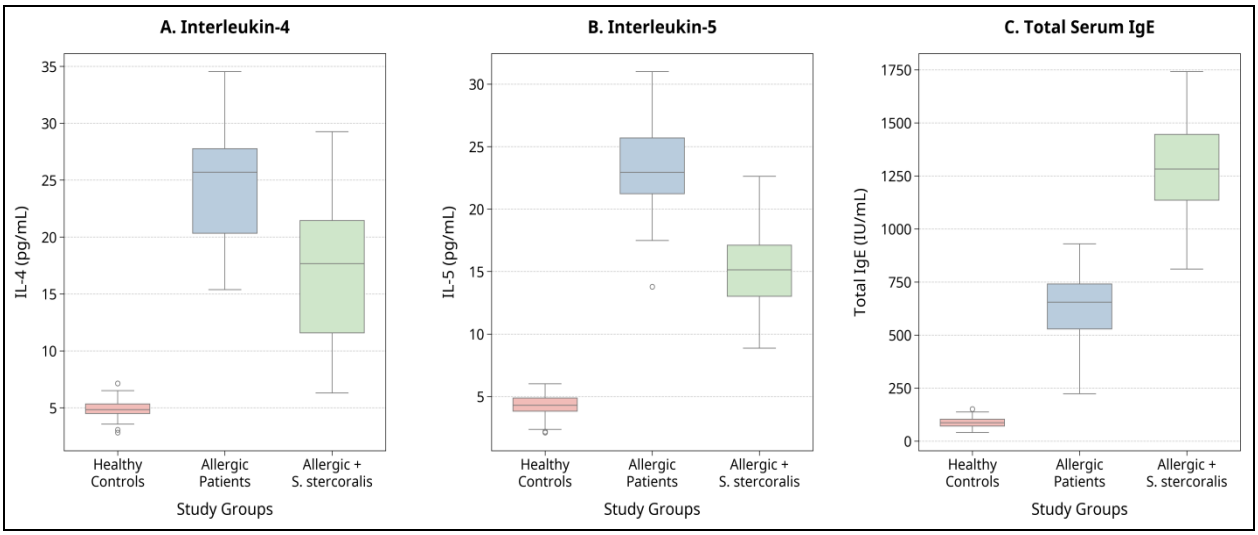

Fig 2: Th2-associated markers. (A) IL-4 levels, (B) IL-5 levels, and (C) total serum IgE

Correlation Analysis

The percentage of Tregs and IL-10 levels showed a strong positive relationship (r = 0.78, P < 0.001), which means that the IL-10 levels are mainly driven by the growth of regulatory T cells in the case of *S. stercoralis* infection (Figure 3).

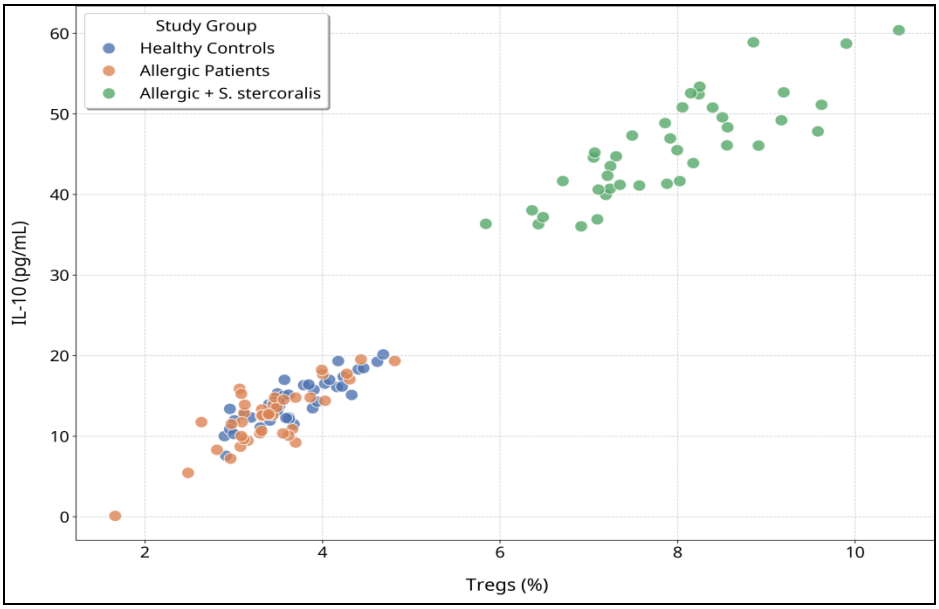

Fig 3: Scatter plot showing the positive correlation between the percentage of regulatory T cells and IL-10 concentration

Discussion

The clinical analytical study presented here gives strong indications of the extensive immunomodulatory effect *Strongyloides stercoralis* infection has on the immunology of the patient with allergic diseases. We have shown that there was a great deal of change in the environment towards a more controlled state with the growth of regulatory T cells (Tregs) and the increased levels of anti-inflammatory cytokines, namely IL-10 and TGF-β. This is commonly known as the helminth-induced immunoregulation phenomenon which seems to conquer the pathological immune response commonly found in asthma, allergic rhinitis and urticaria. The following discussion discusses the mechanisms of these observations, compares our findings with the international literature, and discusses clinical implications of such interactions.

The most significant finding of this study was the remarkable increase of the number of CD4+CD25+FoxP3+ regulatory T cells among allergic patients who were co-infected with *S. stercoralis*. This growth (7.80% ± 1.08%) was two times higher than in allergic patients without the infection (3.30% ± 0.66%). Tregs play a key role in ensuring the immune homeostasis and reducing overactive inflammatory reactions with the release of immunosuppressive cytokines and the cell to cell contact mechanisms [19]. Induction of Tregs by helminths is a documented survival mechanism, which enables the survival of the parasite in the host that may last decades, such as in the autoinfective cycle of *S. stercoralis* [20]. Nevertheless, this regulatory environment is not an allergy-specific one, but rather a bystander effect, which may repress allergic inflammation towards environmental allergens. We obtained data consistent with recent studies indicating that helminth-derived molecules, including the recombinant 14-3-3 protein, has the ability to induce the differentiation of naive T cells in a regulatory phenotype in an active manner [21].

Along with the increase in Tregs, we have witnessed a phenomenal rise in the levels of systemic IL-10 and TGF-β in the co-infected group. IL-10 is a strong anti-inflammatory cytokine, which inhibits the synthesis of pro-inflammatory cytokines, decreases the activation of mast cells and eosinophils, and facilitates the replacement of inflammatory IgG1 by anti-inflammatory IgG4 [22]. This environment is also facilitated by the TGF-β, which induces Treg differentiation and inhibits Th2 activation [23]. The fact that Treg percentages and IL-10 levels are strongly positive (r = 0.78) in our study supports the hypothesis that *S. stercoralis* is a powerful biological inducer of such a regulatory network. This observation can be aligned with the hygiene hypothesis and its current formulation, the old friends hypothesis, the hypothesis holds that the human immune system has become dysregulated due to the extinction of ancient parasites and the resultant increase in allergic and disorders [24].

Interestingly, regulatory markers were increased, whereas Th2-associated cytokines IL-4 and IL-5 were much lower in the AP+SS group than in the AP group. Th2 cell differentiation and IgE switching to a class of antibodies depends on IL-4 and eosinophil recruitment and activation depend on IL-5 [25]. The Th2 arm of the immune response is the characteristic of allergic inflammation and the fact that these cytokines are reduced under the influence of *S. stercoralis* indicates that the regulatory environment provided by this parasite suppresses it. This inhibition of Th2 cytokines offers a mechanistic reason as to why helminth-infected patients usually show less intense allergic reactions despite sensitization to environmental allergens [9]. Recently the involvement of IL-25 and other alarmins in the cascade has been noted, with the IL-25 produced by helminth potentially promoting Treg-mediated suppressive activity in the gut and in the systemic circulation [9].

A primary paradoxes i identified in our results is the marked elevation in total serum IgE levels in the co-infected group (1213.92 ± 249.40 IU/mL), even though the Th2 cytokines were suppressed, and the IL-10 levels were high. It is a complicated phenomenon whereby helminths trigger an enormous and polyclonal production of IgE, which is not necessarily produced against environmental allergens [26]. The surplus, non-specific IgE has been suggested to be able to saturate FcεRI receptors on mast cells and basophils effectively blocking the allergen-specific IgE binding and triggering the degranulation leading to the development of allergic symptoms [11]. Therefore, the high IgE in strongyloidiasis may actually be protective against allergy,

but not cause it. Recent research has underlined that elevated total IgE under the circumstance of helminthiasis is not associated with the severity of clinical allergy, which is essential to clinicians operating in endemic areas [14].

Moreover, we also found that the levels of IFN-γ were also relatively constant in the groups showing that the immunomodulation of *S. stercoralis* targeted the Th2/Treg differentiation, and not a generalized Th1-type of suppression. Such specificity is significant because it implies that the host capacity to initiate Th1-mediated responses to bacterial or viral pathogens may not be affected, though there have been some reports that helminth co-infections may disrupt vaccine responses and control of tuberculosis via IL-10-mediated responses [27]. This balance between protective and pathological inflammation is fragile, and *S. stercoralis* seems to shift the balance to a controlled condition, which helps the parasite survive and, possibly, the allergic state of the host.

These findings have important clinical implications. With the ever-growing prevalence of the allergic diseases in the world, the natural pathways associated with immune regulation may be studied to result in the creation of the so-called helminth-inspired therapies. Recent studies on the excretory-secretory (ES) products of *S. stercoralis* that specific products promote Treg growth and IL-10 generation may offer a template to novel immunotherapeutic agents that can replicate the protective action of the parasite without the adverse effects of a live infection [20]. Furthermore, our paper emphasizes the need to screen patients with so-called refractory or atypical presentation of allergic symptoms in endemic regions since the underlying infection greatly changes the immunological baseline and reaction to conventional treatments, such as corticosteroids [28].

Conclusion

Our research indicates that *Strongyloides stercoralis* infection of patients with allergic diseases stimulates a strong regulatory immune response involving FoxP3+ Treg expansion, and an increase in IL-10 and TGF-β. This regulatory condition efficiently controls the Th2-promoting allergic reaction, with the effect of decreasing the IL-4 and IL-5 levels despite the polyclonal rise in overall IgE. These results offer clinical support of the immunomodulatory capabilities of helm worms and highlight the multifactorial nature of ancient pathogen-modern immune interactions. To establish whether the anthelmintic therapy of such patients causes an increase in allergic symptoms, future longitudinal research is necessary, which would further prove the protective effect of the parasite-induced regulatory network.

Ethical Approval

The study was conducted after obtaining ethical approval from the Basra Health Directorate in accordance with Protocol No. 76 dated April 7, 2025. Verbal informed consent was also obtained from all participating patients.

Conflict of Interest

All authors declare no conflict of interest in this article.

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