Role of IL10 and Total IgE Induced by Helminths Infection in Protection from Allergy among School Children

Nadia El nahas, Nancy Harba and Shaimaa Sharaf

Parasitology Department, Faculty of Medicine, Menoufiya University
dr_nsalah@yahoo.com

Abstract: Epidemiological evidence confirms that helminths infection inversely correlate with allergic manifestations. Its protective effect against allergic diseases was evaluated in this study which carried out on 204 school children aging from 6-14 years old from El shohada center of Menouifiya Governorate. They classified into 113 children representing the urban community and 91 representing the rural community. Comparison of both prevalence of helminths infections and allergic diseases among children was done, and the relationship between each helminths infection and different allergic diseases was also recorded. In addition, the serum level of ; interlukien 10,total IgE were determined in both allergic and parasitic diseases with evaluation of eosinophilia in both conditions. Helminths infections was significantly higher in rural, than in urban areas while the distribution of allergic diseases showed non significant difference between rural and urban children. The occurrence of different types of allergic disease were significantly lower in parasite positive children $p<0.001$. *E. vermicularis* infection was the most prevalent, with significant decrease in allergic manifestation. Also helminths infections produce significant large values of total IgE and IL10 comparing with allergic diseases with significant level of eosinophilia in both conditions. It was concluded that the protective effect of helminths infection may be mediated by high concentration of total IgE suggesting IgE blocking hypothesis and enhanced helminths induced IL10 production with its suppressive effect to allergic response.
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1. Introduction

Helminths infections and allergy are the major health problems in children in many regions with significantly increased prevalence over the past decades especially in developed areas . The relation of helminths infection and allergy association is still controversial whether the intestinal helminths infection can reduce the risk of or exhibit a protective effect on asthma and allergy **(Blackwell *et al.,* 2011 & Kim, 2011).**

The immune response in both helmenths infection and allergic diseases are associated with elevated levels of IgE, tissue eosinophillia, mastocytosis, mucus hypersecretion and CD4+ T cells responses that preferentially secrete Th2 cytokines, IL-4, IL-5 and IL-13 **(Khalifa, 2011).** According to hygiene hypothesis", Improved hygiene, increased vaccinations, antibiotic use and lack of bacterial or viral infections in early life leading to decrease in Th1 response and there might be an elevated Th2 response . This imbalance of the immune responses between Th1and Th2 could be manifested as an increase in susceptibility to helminths infections and allergic disorders **(Fiqueiredo *et al.,* 2010 & Luebert *et al.,* 2011).**

Role of helminths infections in reducing allergy is referred to its strong regulatory effects,they are highly prevalent, and first occur in early life in endemic areas, so may provide a protective mechanism through interference with immune related pathology **(Kamal and Khalifa, 2006 & Mkhize *et al.,* 2011).** It has been suggested that allergic symptoms are low in areas with increasing parasite exposure but high with lower exposure. Helminthes parasites stimulate IgE response and mediate the cytotoxic activity of eosinophilis against larvae. Elevated total IgE antibodies and eosinophils are important components of the immune resistance to allergic manifestations, so the prevalence of atopic diseases in developing countries with high burden of parasitic infections is much lower than industrialized nations **(Erb, 2007).**

Helminthes infection enhanced IL-10 production, which in turn was inversely associated with allergic sensitization. These findings suggest that the anti-inflammatory properties of IL-10 induced by helminthes infection which inhibit the release of histamine by human mast cell may attenuate the allergic response or promote tolerance **(Erb, 2009 & Mkhize *et al.,* 2011).**

The present study aim to determine if parasitic infection offers a protection against allergic diseases or the association between both conditions is dependant on local condition of exposure and sensitization in certain area in Menoufyia Governorate with evaluation of the role of IL-10 and total IgE in controlling the allergy.

2. Subject and Methods

This study was carried out on two hundred four school children aging from 6-14 years old from El

Shohada city and the neighboring villages of Menoufiya Governorates which were divided into two groups: urban group (113) children and rural group (91)

Each child was given two questionnaires :

1- Questions asking about the allergic diseases where the international study of asthma and allergies in childhood (ISAAC) **(Asher *et al.*, 1995)**. These question ask about asthma , allergic rhino conjunctivitis and allergic eczema
2- Questions asking about previous helminths infections and anti helminthic treatment **(Astal, 2004)**.

All children were subjected to the following:

a) Stool examined by direct smear method **(Nascimerito and Moitinho, 2005)** and modified formalin-ether sedimentation technique (**Uga *et al.*, 2010).** Also part of stool was preserved in 2.5 % potassium dichromate for culture by test tube and Agar plate methods for detection of nematode larvae.
b) Pre anal swab **(Nithikathkul *et al.*, 2005)**.
c) Sputum examination **(Cheesbrough, 2004)**.
d) Gimsa stained blood films were made according to **Fleck and Moody (1998)**.
Complete blood count was performed to determine the number of eosinophils using blood cells analyzer.
e) Assessment of IL-10 level and total IgE concentration by ELISA : Serum samples were collected from (43) children with positive helminthes infection and (43)children with positive allergic manifestation in addition to (11)control children, whose were free from any parasitic infection or allergic disease.

Samples were prepared according to **Ceyhan *et al.* (2006)** for measuring of IL-10 by IL-10 ELISA kit (Ani Biotech OY Organism Laboratories Busine Unit) . Total serum IgE concentrations were measured using Accu Bind ELISA Kit (Monobind I nc. Lake Forest CA92630,USA.). According to the manufacture's instructions .The obtained results for serum IgE level were interpretated as more than 208IU/ml indicating higher serum level of total IgE than normal range.

Statistical analysis: collected data were tabulated and analysed using statistical package for social science (SPSS) for windows version 11.0 chi square test was used for comparison between groups . $P<0.05$ was considered statistically significant. Correlation coefficient (r) used for measuring relationship between two attributes , value of r :near zero indicates little correlation ,+1or-1 indicates high level of correlation .

3. Results:

In the present study: prevalence of parasitic infections in rural area was significantly higher than in urban area as shown in table (1) ($p<0.001$). As regards allergic disease, they were lower among rural children but no significant difference was detected, table(2) where the prevalence of asthma, rhino conjunctivitis and eczema were 16.4%, 17.5% and 13.1% respectively in rural and urban areas they were 23.8%, 23.0% and 15%respectivily ($p>0.05$). The distribution of allergic diseases among children having parasitic infections whether in rural or urban children were shown in table (3), the prevalences of different types of allergic diseases were significantly lower in parasite positive children ($P<0.001$). Regarding asthma it was 8.5% in parasite positive children versus 34.5% in parasite negative children ($P<0.001$). Similar results were recorded for rhinoconjunctivitis and eczema in parasite positive children, they were 6.6% and 4.7% respectively, versus 35.3% and 24.2% respectively in parasite negative children ($P<0.001$)

The relationship between each helminthes infection and different allergic diseases in this study shown in graph (1) where allergic manifestations were less frequent among *A. lumbricoides* infected children regarding asthma and rhinoconjunctivitis Instead of this, non of *H. nana* infected children were positive for any kind of allergic disease. On the other hand, allergic diseases were significantly lower in *E. vermicularis* positive children than negative ones. The mean value of IL-10 recorded in this study was significantly higher in parasite infected children comparing with their values in children with allergic manifestation ($P<0.001$) and control children ($P<0.001$) .Table (5). On the other side, the relation was non significant between children with allergic diseases and control children ($P>0.05$) where the mean value of IL-10 in allergic children was 16.99±5.08 and it was 20.71±1.58 in control children (Table 5). Moreover, the correlation between serum level of IL-10 and each parasites in parasitic infected children was positive for *A. lumbricoides, H. nana* and *E. vermicularis* reaching a significant value for *E. vermicularis* infection ($P<0.05$) (Table 4). Meanwhile there was a negative correlation between serum level of IL-10 and different types of allergy without reaching a significant level with any of them.

The results of serum level of total IgE and eosinophilic count, recorded high significant levels in both allergic and parasitic infected children being higher in parasitised children regarding total IgE ($p<0.001$) and in allergic children regarding eosinophillia ($p<0.001$) table (5). The highest level of total IgE concentration was recorded with *A. lumbricoides* infection followed by *H nana* then *E. vermicularis* infections graph(2).

No nematode larvae were detected by test tube or Agar plate culture methods. Also sputum examination and blood films didn't show any positive results for parasitic infections.

Table (1): Prevalence of parasitic infection among rural and urban children.

Parasite	Rural (91)		Urban (113)		X2	*P.* value
	No.	%	No.	%		
A. lumbricoides						
+ve	9	9.9%	3	2.7%	4.77	<0.05
-ve	82	90.1%	110	97.3%		
H. nana						
+ve	12	13.2%	3	2.7%	8.21	<0.001
-ve	79	86.8%	110	97.3%		
E. vermicularis						
+ve	46	50.5%	32	38.3%	41.43	<0.001
-ve	45	49.4%	81	71.7%		

Table (2):Prevalence of allergic diseases among rural and urban children.

Allergic disease	Rural (91)		Urban (113)		X2	*P.* value
	No.	%	No.	%		
Asthma (43)	15	16.4%	28	23.8%	1.69	>0.05
Rhino-conjuctivitis(42)	16	17.5%	26	23.0%	0.91	>0.05
Eczema (29)	12	13.1%	17	15.0%	0.14	>0.05

Table (3):Relation between helminthic infection and allergic diseases.

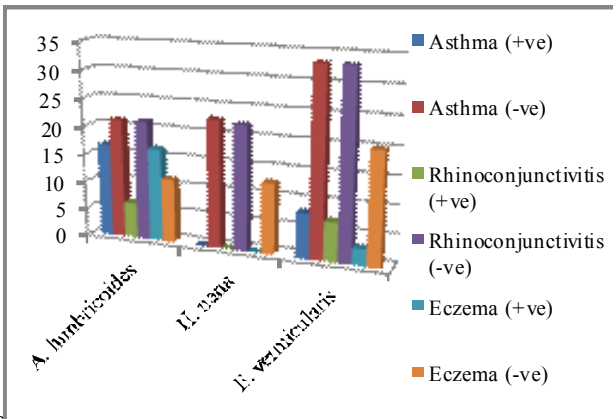
Parasites 204	Asthma 43				X^2	p. value	Rhinoconjunctivits 42				X^2	p. value	Eczema 29				X^2	*p.* value
	No. +ve	%	No. -ve	%			No. +ve	%	No. -ve	%			No. +ve	%	No. -ve	%		
+ve 105	9	8.5	96	91.4	20.2	<0.0	7	6.6	98	93.3	25.6	<0.0	5	4.7	100	95.2	15.8	<0.0
-ve 99	34	34.3	65	65.6			35	35.3	64	64.6			24	24.2	75	75.1		

Table (4): Correlation between IL-10 values in both allergic and parasitic infected children.

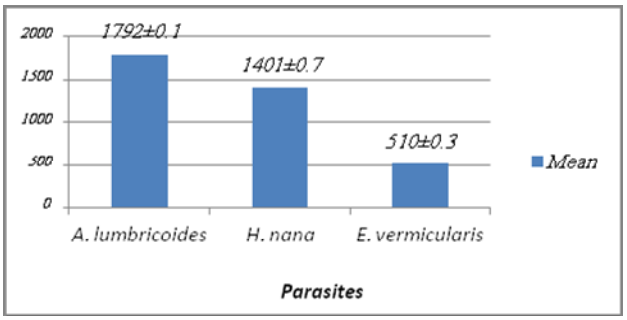
	IL-10	
	R	*P.* value
Allergic disease		
Asthma	-0.20	>0.05
Rhnioconjunctivitis	-0.26	>0.05
Eczema	-0.24	>0.05
Parasites		
A. lumbricoides	+0.34	>0.05
H. nana	+0.19	>0.05
E. vermicularis	+0.58	<0.05

Table (5): Comparison of mean value of IL-10 between parasite infected children, allergic children and control

	+ve parasite (n=43) X±SD	+ve allergy (n=43) X±SD	Control (n=11) X±SD	F. test	*P.* Value
IL-10	35.54±10.59*	16.99±5.08**	20.71±15.8***	32.73	P_1<0.001 (between * & **) P_2<0.001 (between * & ***) P_3>0.05 (between ** & ***)
IgE	1611.2±12.93	980.5±16.83	108.3±1.34	377.62	<0.001
Eosinophilia	23.5±1.43	31.9±0.88	4.6±0.84	659.9	<0.001



Graph (1): Distribution of different allergic diseases in positive and negative ***helminths*** infected children



Graph (2): Distribution of IgE concentration in positive parasitic infected children regarding each parasite

4. Discussion:

The ability of intestinal helminthes to manipulate the immune system of their host towards a Th2 response has been proposed to modulate auto-immune and allergic diseases. There is an ecologic relationship between helminthes infection and development of allergy **(Akdis *et al.*, 2004 & Bodammer *et al.*, 2011)**. Moreover, it was found that helminthes infections are associated with increase of the anti-inflammatory cytokine Il-10 which is deficient in allergic patients **(Kim, 2011)**, so this cytokine may be has a role in regulating the allergic response. In this study, the data were used to explain the hypothesis that helminthes infection are protective or preventive for allergic manifestations, in addition to evaluate the role of IL-10 with its important anti-inflammatory and anti allergic properties in this hypothesis Initially a comparison was made between rural and urban children regarding the prevalence of parasitic infection and allergic diseases. It was found that parasitic infections were significantly higher in the rural than the urban area (P<0.05) **Table (1) ,** mostly due to unsanitary living condition i.e unsanitary water supply, sewage disposal, soil contamination of foods, exposure to animals, insects etc.. In agreement with these findings , **Gamboa *et al.* (2003) & Yami *et al.* (2011)**. Helminthes infections detected in this study in both rural and urban children were, *Ascaris lumbricoides, Hymenolypis nana and Enterobius vermicularis*. It is similar to **Degeye *et al.* (2003)**.

Allergic diseases were higher in urban than in rural children, but didn't reach a significant level **Table(2)**.This can be explain by different environmental factors that affect development of allergy in both communities other than cleanliness like pollution and allergen exposure in according to the explanation of **Caralho *et al.* (2008) & Arnedo *et al.* (2009)**.

Gaur et al. (2006) referred the similarities in prevalence to matching life style in rural and urban population in their area of study. Others found the rate of reversible airway obstruction was higher in the urban than the rural areas **(Obihara *et al.*, 2006 & Ponte *et al.*, 2011)**. Also, **Cooper (2009) - Clavert and Burney (2010)** recorded higher prevalence of asthma and rhinoconjunctivitis in urban than rural areas**.**

The insignificant difference detected in this study for the prevalence of eczema in both rural and urban areas was in agreement with the finding of **Haileamlak *et al.* (2005)** where the rural prevalence of atopic dermatitis was similar to the urban prevalence. In contrary, **Gamboa *et al.* (2003)** reported higher cases of atopic dermatitis in urban area than per urban rural ones.

It was found that the prevalence of allergic disease (asthma, rhino conjunctivitis and eczema) were significantly lower in parasite positive children than parasite negative ones (P < 0.001) **Table (3)**. **Rodrigues *et al.* (2008)** supported these results where they found negative allergen skin sensitivity test among helminths infections.

The relation of eczematous allergic manifestation and parasitic infection in this study were supported by **Schafer *et al.* (2005) & Flohr *et al.* (2008)**, as they found an inverse association between history of having parasite and development of atopic eczema. On the contrary, **Haileamlak *et al.* (2005)** reported that the prevalence of atopic dermatitis tended to be increase in children with intestinal helminthes.

Ripa *et al.* (2010) demonstrated that helminthis infection of low intensity can potentiate the synthesis of Ig.E antibodies against environmental allergen and enhancing the allergic reactivity while the intense helminthic infection can interfere with the allergic response by saturation of mast cells and inhibition of specific IgE synthesis. **Neuza *et al.* (2010)** found that helminthes infection may be a cause of early wheezing in small children with recent or light infection. So, further investigation to study the role of parasites, their soluble antigen, anti parasite anti allergen and cross

reactive antibodies in pathogenesis of allergic disorder should be done.

The present study revealed non significant relation between *A. lumbricoid*es infection and development of allergic manifestation **graph (1).** This result mostly due to low prevalence of *Ascaris* in studied groups and subsequently less potent immunoregulatory mechanisms according to **Cooper *et al.* (2004); Ponte *et al.* (2006) & Neuza *et al.* (2010).**

On the contrary, **Schafer *et al.* (2005); Fallon and Mangan (2007) & Clavert and Burney (2010)** reported an inverse association between *Ascaris* infection and occurrence of wheezes and atopic dermatitis .They refer this to the higher prevalence of *Ascaris* infection recorded in their studies. Another point of view was reported by **Ripa *et al.* (2011)** that low intensity of *Ascaris* infection was associated with increase risk of developing allergic rhino conjunctivitis.

Obihara *et al.* (2006) suggested that mild helminthic infections may leads to no or moderate stimulation of anti – inflammatory networks and this may result in an enhanced reaction to environmental allergens and atopic response. Moreover, **Haileamlak *et al.* (2005)** reported that *Ascaris* infection is not related to atopic dermatitis and they suggested that the reported inverse relation to other allergies e.g. asthma is an organ specific immune suppression rather than generalized immune suppression.

The study revealed that *H. nana* positive children had not any type of allergy but negative children showed asthma and rhino conjunctivits **(Graph 1).** This may be explained by the low prevalence of *H. nana* infection among studied groups also, possibility of frequent or repeated antihelminthic therapy which may explain the absence of the immunoregulatory mechanisms. **Cooper *et al.* , 2004** suggested a protective effect of *H. nana* against all types of atopy. In a case study on a 12 years old girl, she had suffered from repeated allergic attacks. When these attacks had been stopped, parasitological examination revealed *H. nana* eggs in her stool **Marseylia *et al.* (2007).**

The results revealed significant relation to all kinds of allergy being lower in *E. vermicularis* infected children **(Graph 1)**. This significant negative association between *E. vermicularis* infection and allergy was also reported by **Hung *et al.* (2002)** (Asthma and allergic rhinitis) and **Schafer *et al.* (2005)** (atopic dermatitis). On the other side **Wordemann *et al.* (2008)** reported no association between *E. vermicularis* and asthma and developing atopic dermatitis. However these results may be due to their dependence on stool examination which is less sensitive method for *E. vermicularis* diagnosis compared to the tape test used in this study.

Role of IL-10 in helminths infection and allergic disease:

The mean value of IL-10 were significantly higher in parasite positive children (p<0.001) **(Table 5)**. **Turner *et al.* (2008)** found that African children constitutively secrete more immunoregulatory cytokines (IL-10 & TGF.B) under conditions of hyperendemic exposure to intestinal nematodes, *A. lumbricoides* and *T. trichura*, in addition to high cellular proliferative response to their antigens, suggesting that gut nematodes are important mediators of immunoregulation.

This study showed also positive correlation between *A. lumbricoides* and *H. nana* infections and IL-10 serum level. But this relation did not reach a significant level this may be due to lower worm burden and scarce parasitic infections which may affect the level of IL-10 as mentioned by **Ripa *et al.* (2011).** On the other side **Matera *et al.* (2008)** noticed a significant positive relation between *A. lumbricoide*s infection and IL-10 production on stimulation by *A. lumbricoides* antigen. On contrary, **Geiger *et al.* (2002)** found significant elevation of IL-10 in *A. lumbricoides* infected patients than controls. Concerning *E.vermicularis* infection and IL-10 serum level, there was a significant positive correlation (p<0.05) (**Table 4).**

Cooper *et al.* (2008) do not support the hypothesis that intestinal helminthes induced IL-10 expressing regulatory T cells when stimulated with *A. lumbricoide*s antigen. On the other side, the relation of serum level of IL-10 and allergic disease in studied children was negative relationship with P value >0.05 **(Table 4)**. Many studies reported low concentration of IL-10 in allergic patient than normal subjects **(Zhenq *et al.*, 2010)**. Also **Hussein *et al.* (2010)** recorded that IL10 is not sensitive indicator of atopy .The immunological markers of response to allergens in normal and diseased is the result of a balance between allergen – specific IL-10 producing T-reg .cells and allergen – specific Th2 cells.

It was reported that IL-10 secreting allergen – specific T cells represented the predominant subset with significantly high frequency in comparison to IL-10 and IFN-y secreting T cells in healthy individuals and was low in allergic ones. In other contrary studies **Diaz and Allen (2007) & Xu *et al.* (2010)** reported that IL-10 is over expressed in the skin lesions of atopic dermatitis patients.

Regarding total IgE, immunological studies demonstrated that, there are two different IgE responses to helminths infections. The first of these is the host's defensive response to produce IgE specific to parasite antigens. The second response is that the host also exhibits a non-specific Th2 dependent polyclonal synthesis of IgE which results in highly elevated total serum IgE levels in parasitised populations **(Lynch *et al.*, 1999).**In this study the highest serum level of total IgE was reported with *A. lumbricoides* infection then

with *E vermicularis* and the lowest level was with *H .nana* infection similar results were also reported by **Jalalian *et al.* (2004**). In allergic children total IgE was also significantly higher than control children but significantly lower than the parasitic ones. It was reported that the polyclonal stimulus can suppress allergic responses by reducing the production of specific IgE antibody, resulting in an inverse relationship between total and specific serum IgE .The polyclonal IgE also saturates the IgE receptors on mast cells and blocks access to specific IgE, which further inhibits allergic reactions **(Lynch *et al.*, 1993 & 1999).**

This suppressive activity may be the reason for the diminished prevalence of allergic diseases reported in some tropical populations **(Hugal *et al.*, 1993)**. On the other side significant higher eosinophilia reported in this study regarding allergic children than parasitic children may attributed to elevated IL-10 level in serum of children with positive parasitic infection which, in turn, reduce the number of serum eosinophils **(Yazdanbakhsh *et al.*, 2002 & Klion and Nutman, 2004).**

Numerous studies point to the anti-inflammatory properties of IL-10, which can inhibit the release of histamine by human mast cells **(Turner *et al.*, 2008).** Also the down-regulation of the number of eosinophils in circulating blood is a common finding in chronic intestinal parasitic infections as after the migration of intestinal larvae, there is a remarkable reduction in eotaxin, which is essential for chemotaxis and eosinophilia in these patients **(Medeiros *et al.*, 2006).**

Lima *et al.* (2002) in experimental study on *Ascaris suum* observed a reduction in eosinophil count and eosinophil peroxidase in the airways, as well as a marked reduction in IL-4 and IL-5 in the bronchoalveolar lavage.

Conclusion:

It can be concluded that helminths infections are involved in the down –regulation of allergic diseases but association between both diseases is rather dependent on local condition of exposure and sensitization in the area of study. This effect can be attributed to Il-10 which showd marked increase with helminthic infections specially the highly prevalent ones, also polyclonal non specific IgE causing high level of total IgE which has important role in reducing the allergic manifestation.

Corresponding author
Nadia El nahas
Parasitology Department, Faculty of Medicine, Menoufiya University
dr_nsalah@yahoo.com

References:

Akdis M, Verhagen J, Taylor A, Karamloo F, Karagiannidis C, Crameri R, Thunberg S, Deniz G, Valenta R, Fiebig H, Kegel C, Disch R, Schmidt-Weber CB, Blaser K, Akdis CA. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells J Exp Med. 2004 Jun 7;199(11):1567-75.

Arnedo PA, Barberà J, Bellido JB, Pac-Sa MR, Cruañes JB, Sivera A, Recatalá L. Risk factors and prevalence of asthma in schoolchildren in Castellon (Spain): a cross-sectional study. Allergol Immunopathol (Madr). 2009 May-Jun;37(3):135-42.

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995 Mar;8(3):483-91.

Astal Z. Epidemiological survey of the prevalence of parasites among children in Khan Younis governorate, Palestine. Parasitol Res. 2004 Dec;94(6):449-51. Epub 2004 Oct 28.

Blackwell AD, Gurven MD, Sugiyama LS, Madimenos FC. Evidence for a peak shift in a humoral response to helminthes:Age profiles of IgE in the shuar of Ecuador. PLos Negl Trop Dis; (2011), 5(6):e1218.

Bodammer P, Waitz G, Loebermann M. *Shistosoma mansoni* Infection but not egg antigen promotes recovery from colitis in outbredNMRI mice, Dig Dis Sci (2011); 56:70-78.

Carvalho L, Sun J Kane C, Marshall F, Krawczyk C, Pearce EJ (2008): Review series on helminthes, immune modulation and the hygiene hypothesis: Mechanisms underlying helminth modulationof dendritic cell function .Immunology; 126: 28-34.

Ceyhan BB, Enc FY, Sahin S. IL2 and IL10 levels in induced sputum and serum samples of asthmatics. J Investig Allergol Clin I mmunol; (2004), 14(1):80-5.

Cheesbrough MO. Parasite logical test. In: Cheesbrough, MO (ed). District laboratory diagnosis of tropical countries, 1st edition, Cambridge University press.United Kingdom.p:3-37.

Clavert J and Burney P. Ascaris ,Atopy ,and exercise-induced bronchoconistriction in rural and urban south Africa children. J Allergy Clin Immunol, (2010) 125(1):100-5.

Cooper PJ, Chico ME, Rodrigues LC, Strachan DP, Anderson HR, Rodriguez EA, Gaus DP, Griffin GE. Risk factors for atopy among school children in a rural area of Latin America. Clin Exp Allergy. 2004 Jun;34(6):845-52.

Cooper PJ, Mitre E, Moncayo AL, Chico ME, Vaca MG, Nutman TB. Ascaris lumbricoides-induced

interleukin-10 is not associated with atopy in schoolchildren in a rural area of the tropics. J Infect Dis. 2008 May 1;197(9):1333-40.

Cooper PJ. Interactions between helminth parasites and allergy. Curr Opin Allergy Clin Immunol. 2009 February; 9(1): 29–37.

Dagoye D, Bekele Z, Woldemichael K, Nida H, Yimam M, Hall A, Venn AJ, Britton JR, Hubbard R, Lewis SA. Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. Am J Respir Crit Care Med. 2003 May 15;167(10):1369-73. Epub 2003 Jan 24.

Diaz A, Allen JE . Mapping immune response profiles: The emerging scenario from helminth immunology. Eur J Immunol;(2007), 37:3319-26.

Erb KJ. Can helminthes or helminth-derived products be used in humans to prevent or treat allergic diseases?. Trends in Immunol; (2009), 30:75-82.

Erb, KJ. Helminths, allergic disorders and IgE-mediated immune responses:where do we stand?. Eur. Immunol ; (2007), 37:1170-1173.

Fallon PG, Mangan NE. Suppression of Th2-type allergic reactions by helminth infections. Nature Rev Immunol. 2007;7:220–230.

Fiqueiredo CA, Barreto ML, Rodriques LC, Cooper PJ, Silva NB, et al. (2010): Chronic intestinal helminth infections are associated with immune hyporesponsiveness and induction of a regulatory network; Infect. Immun; 78(7): 3160-7.

Fleck SL, and Moody AH. Blood parasites in Fleck S.L. and Moody A.H. (eds). Diagnostic techniques in medical parasitology.1st edition Wright company L.td. London p: 60.

Flohr C, Quinnellw RJ, Britton J (2008): Do helminth parasites protect against atopy and allergic disease? Clin Exp Allergy; 39: 20-32.

Gamboa MI, Basualdo JA, Córdoba MA, Pezzani BC, Minvielle MC, Lahitte HB. Distribution of intestinal parasitoses in relation to environmental and sociocultural parameters in La Plata, Argentina. J Helminthol. 2003 Mar;77(1):15-20.

Gaur SN, Gupta K, Rajpal S, Singh AB, Rohatgi A. Prevalence of bronchial asthma and allergic rhinitis among urban and rural adult population of Delhi. Indian J. Allergy Asthma Immunol, (2006); 20(2): 90-97.

Hagel I, Lynch N, Perez M, *et al.* Modulation of the allergic reactivity of slum children by helminthic infection. Parasite Immunol 1993; 15:311–5.

Haileamlak A, Dagoye D, Williams H, Venn AJ, Hubbard R, Britton J, Lewis SA. Early life risk factors for atopic dermatitis in Ethiopian children. J Allergy Clin Immunol. 2005 Feb;115(2):370-6.

Hung SL, Tsai PF, Yeh YF. Negative association of Enterobius infestation with asthma and rhinitis in primary school children in Taipei. Clin Exp Allergy. 2002 Jul;32(7):1029-32.

Hussein PY, Zahran F, Ashour WA, Ibrahiem MM, Shalaby SM. Interleukin 10 receptor alpha submit (IL-10RA) gene polymorphism and IL10 serum levels in Egyptian atopic patients. (2010), J Investig Allergol Cin Immunol; 20(1):20-6.

Jalalian M, Rezaiian M, Kia EB, Massoud J. Relation between serum IgE and intestinal parasites .Iranian J public Health, (2004); 33(1):18-21.

Kamal SM, Khalifa KE (2006): Immune modulation by helminthic infections: worms and viral infections parasite .Immunol; 28:484-96.

Khalifa KE (2011): Characteristices and consequences of the immune response to helminthes. PUJ; 4(1):15-28.

Kim DW. Helminth Parasites and Allergic Disease in Vietnam: Do Gut Worms Protect against Allergic Sensitisation, Asthma, Eczema, and Hay Fever? Korean J Parasitol. 2011 June; 49(2): 199–200.

Klion AD, Nutman TB. The role of eosinophil in host defense against helmint parasites. J Allergy Clin Immunol. 2004; 113:30-6.

Lima C, Perini A, Garcia ML, Martins MA, Teixeira MM, Macedo MS. Eosinophilic inflammation and airway hyper-responsiveness are profoundly inhibited by a helminth (*Ascaris suum*) extract in a murine model of asthma. Clin Exp Allergy. 2002; 32:1659-66.

Luebert ED, Noelle L, Svenja S, Hartman S (2011): Modulation of specific and allergy-related immune responses by helminthes .J Biomed Biotechnology; 2011: 821578.

Lynch NR, Goldblatt J, Sowf PN. Parasite infection and the risk of asthma and atopy. Thorax, (1999); 54: 659-660.

Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R, Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol. 1993 Sep; 92(3):404-11.

Marseglia GL, Marseglia A, Licari A, Castellazzi AM, Ciprandi G. Chronic urticaria caused by Hymenolepis nana in an adopted girl. Allergy. 2007 Jul; 62(7): 821-2.

Matera G, Giancotti A, Scalise S, Pulicari MC, Maselli R, *et al.* (2008): Ascaris lumbricoides- induced suppression of total and specific IgE responses in atopic subjects is interleukin 10 – independent and associated with an increase of CD25(+) cells. Diagn Microbiol Infect Dis; 62(3):280-6.

Medeiros D, Silva AR, Rizzo JA, Motta ME, Oliveira E. Relationship between Serum IgE and Intestinal Parasites. Iranian J Publ Health, (2004); 33 (1): 18-21.

Mkhize ZL, Taylor M, Jooste D, ABASO ML, Walzi G (2011): The influence of different helminth infection phenotypes on immune responses against HIV in co-infected adults in South Africa; BMC Infect Dis. 14; 11: 273.

Nascimento SA, Moitinho M L. Blastocystis hominis and other intestinal parasites in a community of Pitanga City, Paraná State, Brazil. Rev Inst Med Trop Sao Paulo. 2005 Jul-Aug; 47(4):213-7.

Neuza M, Alcantara N, Samue JB, Mariese CA. The presence of serum anti-*Ascaris lumbricoides* IgE antibodies and of *Trichuris trichiura* infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children. Respir Res, (2010); 11(11): 114.

Nithikathkul C, Akarachantachote N, Brodsky M, Sukthana Y. Impact of health educational programmes on the prevalence of entrobiasis in schoolchildren in Thailand. J Helminthol, (2005); 79:61-65.

Obihara CC, Beyers N, Gie RP, Hoekstra MO, Fincham JE, Marais BJ, Lombard CJ, Dini LA, Kimpen JL. Respiratory atopic disease, Ascaris-immunoglobulin E and tuberculin testing in urban South African children. Clin Exp Allergy. (2006) May; 36(5):640-8.

Ponte E, Lima F, Araujo MI, Oliveira RR, Cruz AA. Skin test reactivity and Der-p induced IL10 production in patients with asthma or rhinitis infected with Ascaris. Ann Allergy Asthma Immunol; (2006), 96:713-718.

Ponte JC, Junqueria SB, Veigq RV, Barreto ML, Pontes DC. A study on the immunological basis of the dissociation between type 1 hypersensitivity skin reactions to tropicals antigens and serum anti-B-tropicals IgE antibodies, BMC Immunol; (2011), 1;12(1): 34.

Ripa C, Bahnea R, Cojocaru L, Luca MC. Atopic diseases and intestinal helminths .Rev Med Chir Sco Med Nat Lasi ; (2010), 114(4):1017-21.

Ripa C, Bahnea RG, Cojocaru L, Luca MC, Leon M. Sensitisation to Ascaris lumbricoides and asthma severity in children . Rev Med Chir Sco Med Nat Lasi ;(2011), 11(2):387-91.

Rodrigues LC, Newcombe PJ, Cunha SS, Alcantara-Neves NM, Genser B, Cruz AA, Simoes SM, Fiaccone R, Amorim L, Cooper PJ, Barreto ML; Social Change, Asthma and Allergy in Latin America. Early infection with Trichuris trichiura and allergen skin test reactivity in later childhood. Clin Exp Allergy. 2008 Nov;38(11):1769-77. Epub 2008 Jun 10.

Schäfer T, Meyer T, Ring J, Wichmann HE, Heinrich J. Worm infestation and the negative association with eczema (atopic/nonatopic) and allergic sensitization. Allergy. 2005 Aug; 60(8):1014-20.

Turner JD, Jackson JA, Faulkner H, Behnke J, Else KJ, Kamgno J, Boussinesq M, Bradley JE. Intensity of intestinal infection with multiple worm species is related to regulatory cytokine output and immune hyporesponsiveness. J Infect Dis. 2008 Apr 15; 197(8):1204-12.

Uga S, Tanaka K, Iwamoto N. Evaluation and modification of the formalin-ether sedimentation technique. Trop Biomed; (2010) ,27(2):177-84.

Wördemann M, Diaz RJ, Heredia LM, Collado Madurga AM, Ruiz Espinosa A, Prado RC, Millan IA, Escobedo A, Rojas Rivero L, Gryseels B, Gorbea MB, Polman K. Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. Trop Med Int Health. 2008 Feb; 13(2):180-6.

Xu YQ, Gao YD, Yanq J, Guo W. A defect of CD4+ CD25+ regulatory T cells in inducing interleukin 10 production from CD4+ T cells under CD46 co stimulation in asthma patients. (2010) J Asthma; 46(4): 367-73.

Yami A, Mamoy Y, Kebede S. Prevalence and predictors of intestinal helminthiasis among school children in Jimma zone;a cross-sectional study .Ethiop J Health Sci; (2011), 21(3):167-74.

Yazdanbakhsh M, Kremsner PG, Van RR. Allergy parasites and the hygiene hypothesis. Science, (2002), 296: 490-494.

Zhenq XQ, Li CC, Lin A, Yan WH. Analysis of the plasma soluble human leukocyte antigen –G and interleukin -10 level in childhood atopic asthma.(2010). Hum Immunol 71(10):982-7.

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