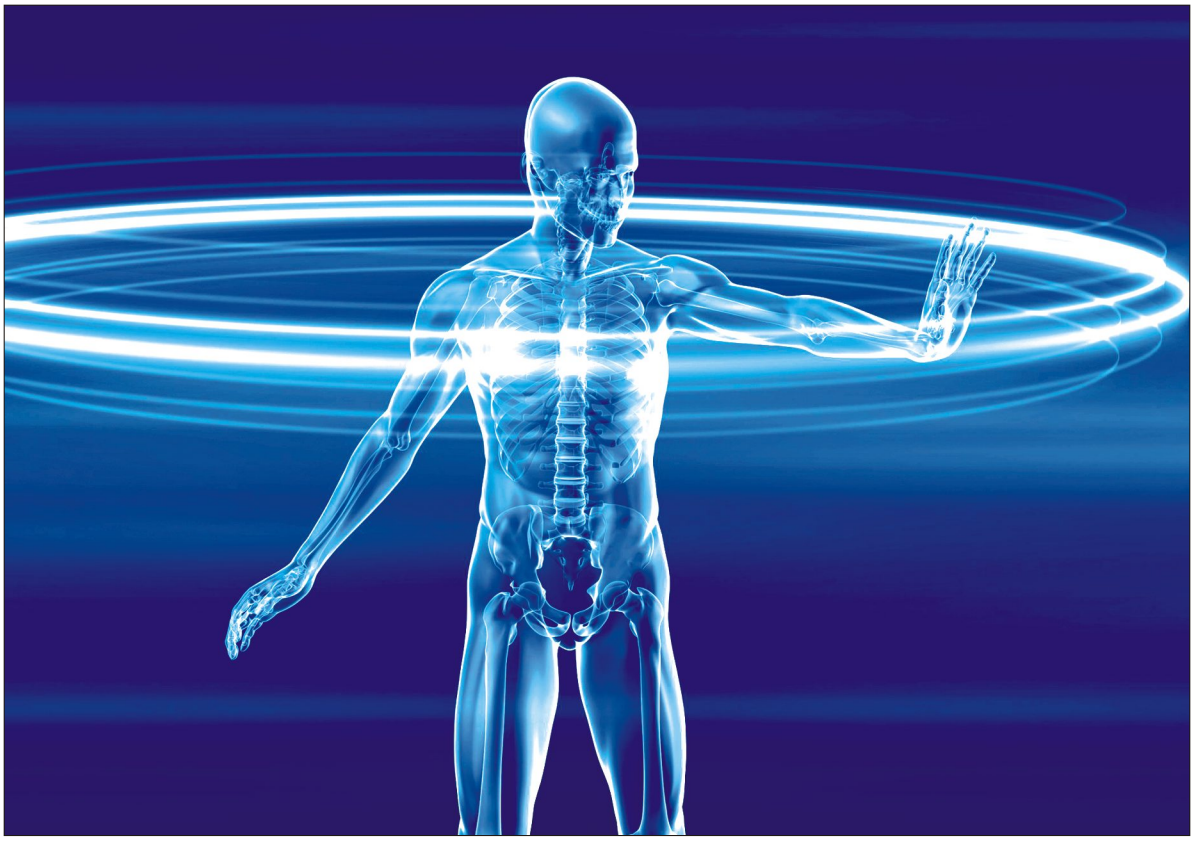

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Research Article
Helminth Infection as Immunomodulator and Therapeutic Agent Against Rheumatoid Arthritis

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Abstract

Background and Objective: It is hypothesized that helminthic parasites have regulatory effects on auto-immune diseases exhibited through a highly active immune response. This study aims to ascertain the effect of both arthritis and helminths on the immune system of patients to enable further immunological insight into their association which can promote multiple management options. **Materials and Methods:** Total 100 patients with Rheumatoid arthritis infected with Helminthic parasites in Jos, Nigeria from January-September, 2019. Ethical approval and patient consent were obtained. Concentration and wet preparation methods were used for stool samples for parasites identification. About 3 mL of EDTA blood was used for CD4 count using cyflow, Eosinophil count using both automated method and peripheral blood film method. The data obtained were analyzed by SPSS software version 22. **Results:** Multiple comparisons of Eosinophil and CD4 in rheumatoid arthritis and helminths co-infection every 6 weeks for 9 months is highly significant ($p<0.001$) establishing the high presence of helminths infection in causing an immunomodulatory effect of CD4. **Conclusion:** The finding of this study showed that helminths infection improves the immunological system thereby diminishing the effect of rheumatoid arthritis. Therefore, the helminths parasite can be used for the management of rheumatoid arthritis. It is also recommended that more research should be carried out to harvest the immunological property of these helminth organisms and helminth organisms should be seen as symbiotic organisms, not a parasite.

Key words: Helminths parasite, rheumatoid arthritis, immunomodulatory, eosinophil, CD4, therapeutic agent, cytokines

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The major roles of the immune system are foreign antigens removal, immunologic memory composition and tolerance to self-antigens advancement. The major types of lymphocytes are T-lymphocytes (thymus-derived lymphocytes), B-lymphocytes (bone-marrow-derived) and the natural killer cells (NK cells)[1].

Cellular immunity is mediated by T-lymphocytes along with humoral immunity being mediated by B lymphocytes to give adaptive immunity, which functions in close association with the innate immune system. The maturation of B-lymphocytes takes place in the bone marrow while the maturation of T-lymphocytes needs the thymus, before being released to the peripheral lymphoid organs for further antigen-mediated differentiation. The majority of T-lymphocytes are made of CD4+T and CD8+T[1]. CD4+cells differentiate into a small subset on release from the thymus to peripheral lymphoid organs such as natural killer T cells (NKT cells) and natural regulatory cells. When CD4+T cells is activated, it will separate into different effector subtypes which play a major role in mediating immune response via the secretion of specific cytokines. The CD4+T cells have collaborative functions which include the following: activation of B-lymphocytes, cytotoxic T cells, innate immune cell system, nonimmune cells likewise function in the suppression of immune reaction[1].

There are two major types of arthritis namely; Osteoarthritis (OA) and Rheumatoid Arthritis (RA). Inflammation of the joints is the main feature of this disease condition. Osteoarthritis (OA) is common in old age with a feature of depressed and degenerative immunological disease which is controlled by an early innate response from a Cascade of immune reactions characterized by joint stiffness, pain or inflammation[2,3]. "Rheumatoid arthritis is a chronic autoimmune inflammatory joint disease affecting the synovial joints and other connective tissues and associated with loss of function from joint deformity arising from cartilage and bone destruction resulting in a significant reduction in quality of life"[3]. It is common among young age (20-40 years) with a female gender being more in number[3]. The pathogenesis of Rheumatoid arthritis is as a result of the inability to differentiate self from non-self and complicated malfunction and deformed immune responses to environmental insults[4,5].

The helminth infection has surpassed a third of the universal population majorly found among developing countries which caused a wide range of asymptomatic to depressing diseases arising from tissue or intestinal infestation and often time be chronic lasting as long as 20 years[2,6,7]. Helminths are essentially multicellular eukaryotic parasitic organisms of 3 taxonomic groups namely, cestodes or tapeworms, nematodes or roundworms and trematodes or flukes[6,8]. Helminth ability to infect depends on various ways such as their mode of transmission which can be fecal-oral, transcutaneous or through arthropod vectors; different intermediate or definitive hosts ranging from mollusks, fish, birds, arthropods, mammals; various infection sites in the body, long term survival, etc., all giving rise to different clinical presentations[6,9]. The characteristic feature of all helminthic infections in both animals and humans is the presence of peripheral and intestinal eosinophilia[10].

Previous research indicated that helminthic parasites have immunomodulatory properties by altering or halting the immune system to reduce immune responses with infected persons exhibiting immunologic hypo-responsiveness[7,11,12]. It is hypothesized that "helminthic parasites have regulatory effects on auto immune diseases exhibited through a highly active immune response by suppressing the T helper type 1 and 2 cells and stimulating the T regulatory cells which in turn releases inflammatory inhibiting substances, activates cells that provoke potent IgE responses and macrophage induction all of which reduce inflammation in the body leading to less severe auto immune diseases from immunologic tolerance"[12,13,14]. Subsequent studies further showed that such helminthic infected persons who displayed immunologic tolerance; show recovered antigen-specific response following parasite clearance by taken anti-helminthic drugs which indicates that the antigen-specific immune response inhibitions were likely due to the pre-existing Helminths infection[7,15].

This study aims to ascertain the effect of both arthritis and helminths on the immune system of patients to enable further immunological insight into their association which can promote multiple management options.

MATERIALS AND METHODS

Study area: This case study was conducted on 100 patients with Rheumatoid arthritis patients infected with Helminthic parasites in Jos and its environs, Plateau State, Nigeria from January-September, 2019.

Ethical approval: Ethical approval and patient consent statements were taken from everyone and the study was performed in the Medical Laboratory Department of DEE medical center.

Research protocol: Samples were collected from asymptomatic individuals confirmed with helminths parasitic infection and rheumatoid arthritis every 6 weeks knowing that significant change in the immune system takes places every 6 weeks[16]. Individuals in haste to take anti-helminth drugs or those that have taken were excluded from the study.

Stool samples collected were used to identify the parasite using the concentration method and wet preparation. Total 3 mL of individual blood were put into the EDTA bottle and were used for CD4 count using cyflow and Eosinophil count using both automated method and peripheral blood film method.

Statistical analysis: The data obtained were analyzed by SPSS software version 22.

RESULT

Rheumatoid arthritis patients infected with Helminthic parasites were studied with 30% male, 70% female and mean age was 36.32±13.3 years as shown in Table 1.

Table 2 shows the Mean of eggs per gram of feces and the percentage (%) of helminthic parasites are as follows: *Ascaris lumbricoides*: 411.11±242.32 (27), Hookworm (*Necator americanus*): 344.44±247.87 (18), *Strongyloides stercoralis*: 340.00±183.79 (10), *Trichuris trichiura*: 344.44±200.69 (9) *Schistosoma mansoni*: 420.00±226.18(20), Taenia species: 550.00±289.83 (16).

Table 3 result shows a high significant difference (p = 0.000, 0.005) of the great effect of rheumatoid arthritis and helminths co-infection on CD4 count for every 6 weekly for 9 months indicating the relevance of helminthic infection improving the immunological system thereby diminishing the effect of rheumatoid arthritis.

Multiple comparisons of CD4 in rheumatoid arthritis and helminths co-infection every 6 weekly for 9 months is highly significant (p = 0.000) as shown in Table 4 establishing the immunomodulatory effect of CD4 as a result of helminthic infection.

Table 5 result shows a highly significant difference (p = 0.000, 0.018) of the great effect of rheumatoid arthritis and helminths co-infection on Eosinophil count for every 6 weekly for 9 months indicating the high presence of helminthic infection in all the patients used for the study.

Multiple comparison of Eosinophil in rheumatoid arthritis and helminths co-infection every 6 weekly for 9 months is highly significant (p = 0.000, 0.001) as shown in Table 6 establishing the high presence of helminthic infection in causing an immunomodulatory effect of CD4.

We hypothesize that helminthic infection is not an immunomodulator and therapeutic agent against rheumatoid arthritis. We reject our null hypothesis based on the results

Table 1: Demographic and clinical characteristic of rheumatoid arthritis patients with helminth parasitic infestation

Characteristic	Total of patients	Number of percentage
Number of patients	100	
Ages (years)		
18-30	35	35
31-43	55	55
44-55	10	10
Mean age		
36.32±13.3 years		
Gender		
Male	39	30
Female	17	70

Table 2: Mean and percentage distribution of helminth parasite in the study population

Helminths parasite	Mean±SD (eggs per gram of faeces)	Percentage (%)
Ascaris lumbricoides	411.11±242.32	27
Hookworm (*Nectar americanus*)	344.44±247.87	18
Strongyloides stercoralis	340.00±183.79	10
Trichuris trichiura	344.44±200.69	9
Schistosoma mansoni	420.00±226.18	20
Taenia species	550.00±289.83	16

Table 3: General effect of rheumatoid arthritis and helminths co-infection on CD4 count for every 6 weeks for 9 months

Source	Type III sum of squares	df	Mean square	F	p-value
Corrected model	21439950.017	10	2143995.002	486.943	0.000
Intercept	259080976.309	1	259080976.309	58842.280	0.000
Parasites	74479.244	5	14895.849	3.383	0.005
Weeks	21365470.773	5	4273094.155	970.502	0.000
Error	2593351.156	589	4402.973		
Total	321211444.000	600			
Corrected total	24033301.173	599			

df: degree of freedom

Table 4: Multiple comparisons of CD4 in rheumatoid arthritis and helminths co-infection every 6 weeks for a period 9 months

Weeks	Mean difference	Std. Error	p-value
1-2	-111.760	9.384	0.000
1-3	-226.500	9.384	0.000
1-4	-317.820	9.384	0.000
1-5	-427.700	9.384	0.000
1-6	-564.620	9.384	0.000
2-3	-114.740	9.384	0.000
2-4	-206.060	9.384	0.000
2-5	-315.940	9.384	0.000
2-6	-452.860	9.384	0.000
3-4	-91.320	9.384	0.000
3-5	-201.200	9.384	0.000
3-6	-338.120	9.384	0.000
4-5	-109.880	9.384	0.000
4-6	-246.800	9.384	0.000
5-6	-136.920	9.384	0.000

Table 5: General effect of rheumatoid arthritis and helminths co-infection on Eosinophil count for every 6 weeks for 9 months

Source	Type III sum of squares	df	Mean square	F	p-value
Model I	24101.658	11	2191.060	2475.410	0.000
Parasites	12.148	5	2.430	2.745	0.018
Weeks	2260.908	5	452.182	510.865	0.000
Error	521.342	589	0.885		
Total	24623.000	600			

Table 6: Multiple comparisons of Eosinophil in rheumatoid arthritis and helminths co-infection every 6 weeks for a period of 9 months

Weeks	Mean difference	Std. Error	p-value
1-2	-2.170	0.133	0.000
1-3	-3.470	0.133	0.000
1-4	-0.450	0.133	0.001
1-5	1.180	0.133	0.000
1-6	2.320	0.133	0.000
2-3	-1.300	0.133	0.000
2-4	1.720	0.133	0.000
2-5	3.350	0.133	0.000
2-6	4.490	0.133	0.000
3-4	3.020	0.133	0.000
3-5	4.650	0.133	0.000
3-6	5.790	0.133	0.000
4-5	1.630	0.133	0.000
4-6	2.770	0.133	0.000
5-6	1.140	0.133	0.000

and accept our alternative hypothesis that helminthic infection is an immunomodulator and therapeutic agent against rheumatoid arthritis.

DISCUSSION

This study shows that helminthic parasites improve the immune system and can also be used as a therapeutic agent in the treatment of rheumatoid arthritis. It is in agreement with Immune modulation theories that illustrate the helminths and immunity relationships involving these two theories namely: co-evolution and hygiene[13,17].

Co-evolution theory postulated "that humans adapted to helminths parasitic infections over a long period of global underdevelopment with the human body maintaining an asymptomatic stance from immune tolerance of the helminths infections by allowing the antigens regulate the immune system and manifested as a protective effect on allergies, asthma, autoimmune conditions such as arthritis, inflammatory bowel disease, multiple sclerosis etc"[7].

Nevertheless, abnormal control of immune modulation in advanced medical science when anti-helminthic medications were introduced makes such a protective effect to diminish[7,15].

Another study that supports the immune modulation co-evolution theory was when arthritic-induced mice were infected with Schistosoma Mansoni parasites, less arthritic symptoms were noticed[11]. More studies by other researchers, one of which came to conclude that helminthic parasite

infection is protective of rheumatoid arthritis[18]. Another study confirmed that helminthic parasites acquired modulatory effect on the innate immunity which "impedes the development of aberrant immunity" and that a decrease in Helminths infection mostly observed in more developed countries has resulted in an increased prevalence of inflammatory diseases, arthritis inclusive[19].

The hygiene theory pointed to "the higher prevalence of allergy and auto immune diseases in more developed nations than their developing counterparts which it attributes to a higher standard of living which favored a reduced prevalence of Helminths infection and a higher allergenic propensity than the lesser hygienic nations which have a higher Helminths infection propensity from a lower living standard"[6,12,17] Hence, Nigeria is still a developing country where the study was carried out. This imply that developing countries with less hygienic will have higher helminths infection thereby increasing the immunological system of the rheumatoid arthritis patients and reducing allergy and autoimmune disease. Anti-helminth drugs should be discouraged in such areas. This research study could not cover the immunological properties of these helminth organisms; therefore we recommend further research to harvest the immunological property of these helminth organisms for the management of other diseases that need immunotherapy.

CONCLUSION

Our finding shows that significant change in the immune system takes place every 6 weeks. We also discover that helminths infection improves the immunological system thereby diminishing the effect of rheumatoid arthritis.

SIGNIFICANCE STATEMENT

This study discovered that the helminthic parasite can be used as an immunomodulator and treatment for rheumatoid arthritis since it is an autoimmune disease. Therefore, we will advocate that Helminths organisms should not be called parasite but symbiotic organisms.

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