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Immunological and Biochemical Glimpses of Giardiasis in Thalassemic Patients

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ABSTRACT

Aims The present work seeks to ascertain immunological and biochemical characteristics in thalassemic individuals who have contracted giardiasis.

Materials & Methods This experimental study was conducted at the Thalassemia Center in Thi-Qar province, Iraq, in 2022. Fifty patients (21 males and 29 females) and 20 healthy controls were investigated. Of the patients' group, twenty-five were thalassemic and had giardiasis. The other 14 patients were thalassemic and free of giardia infection, and the remaining 11 patients were non-thalassemic but had giardia infection. Five ml of venous blood from each participant was withdrawn to determine WBCs, neutrophil activity, and levels of IL-6, iron, ferritin, and transferrin.

Findings The levels of interleukin-6 in the three patient groups (28.20, 23.29, and 30.94pg/ml) were considerably higher than those in healthy controls (16.09pg/ml). In patient groups, there was a notable rise in WBCs but a notable fall in neutrophil activity. Additionally, a substantial increase in iron and ferritin was found, although transferrin was lower in the patients than in the control group.

Conclusion The thalassemia and giardia patients have greater iron and ferritin levels but much lower transferrin levels than the healthy individuals.

Keywords Thalassemia; *Giardia lamblia*; Iron; Ferritin; Transferrin

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Introduction

In many regions of the globe, intestinal parasite diseases cause high rates of morbidity and death, making them a worldwide issue [1]. The most prevalent intestinal protozoan parasites include Giardia intestinalis, Entamoeba histolytica, Cyclospora cayetanenensis, and Cryptosporidium spp. These parasites are responsible for diseases known as giardiasis, amoebiasis, cyclosporiasis, and cryptosporidiosis, respectively, all of which are associated with diarrhea [2]. Giardia intestinalis stands out as the most common parasitic cause of diarrhea in both developed and developing nations [3].

Giardiasis is a well-known gastroenteritis caused by the flagellate protozoan parasite *Giardia lamblia* [4]. It is a leading cause of enteric infections worldwide, with a higher prevalence in developing and low-income countries [1, 5]. A wide range of clinical symptoms, including vomiting, stomach discomfort, weight loss, severe diarrhea, and malabsorption syndrome, are what set the condition apart [6].

Giardia duodenalis, also referred to as Giardia lamblia or Giardia intestinalis, is a flagellate parasite responsible for widespread epidemic or sporadic diarrhea globally. In developing nations, the infection rate can reach up to 30%, while in developed countries, it may be around 7% [7]. Notably, in developed regions, Giardia is the primary cause of parasitic diarrhea [8]. The parasite exists in two forms: the active trophozoite form and the infective cyst form. Human infection typically occurs through ingestion of Giardia duodenalis cysts present in fecal-contaminated water or food. These cysts are oval-shaped, ranging from 8 to 18 µm by 7 to 10 µm, and contain four nuclei. They are resilient and can endure harsh conditions, surviving in cold water for up to three months. Upon ingestion, the cysts encounter gastric acid, bile, and trypsin in the duodenum. As they reach the proximal small intestine below the level of the ampulla of Vater, excystation takes place, releasing trophozoites (two trophozoites per cyst) [9]. Trophozoites measure between 9 and 21 µm in length, 5 and 15 µm in width, and 2 and 4 µm in thickness. They possess two large nuclei, a median-pear-shaped body, one ventral sucking/adhesive disc, and eight flagellae. Many trophozoites attach to the brush borders of enterocytes using their adhesive discs, while others remain in the duodenal lumen. They reproduce through binary fission, resulting in numerous trophozoites. These trophozoites migrate toward the distal small bowel, where encystation occurs. The cysts then pass through the colon and are excreted in stool, becoming immediately infectious [10].

This condition is considered a major threat to public health, particularly in vulnerable populations, including children and individuals with impaired immune systems [11]. Patients with low stomach acidity, X-linked agammaglobulinemia, chronic pancreatitis, common variable immunodeficiency, and protein-energy malnutrition have all been shown to be predisposed to giardiasis [12].

Susceptibility to giardiasis has been observed in individuals with common variable immunodeficiency, X-linked agammaglobulinemia, diminished gastric acidity, chronic pancreatitis, and protein-energy malnutrition [13].

Beta-thalassemia major, one of the most prevalent hemoglobinopathies, is not connected to a basic immune deficiency. However, minor immunological dysfunction has been noted [14], and secondary immunological dysfunction arises due to iron overload and the phagocytosis of red blood cells (RBCs) in the spleen by macrophages, leading to chronic immune stimulation. This dysfunction is characterized by a reduced CD4/CD8 ratio and impaired function of neutrophils, macrophages, and natural killer (NK) cells. Elevated immunoglobulin levels with poor differentiation have also been reported. These factors may predispose patients to various types of infections [15].

The occurrence of infections in people with thalassemia and the function of the immune response to infection are unknown [16]. Susceptibility to infections in thalassemia and sickle cell disease (SCD) arises from a wide range of immunological abnormalities and exposure to infectious agents. To simplify the intricate scenario of immune system disruptions, four fundamental issues can be addressed: the disease itself, encompassing all inherent changes in the pathological process that may interfere with the immune system, iron overload (IOL), transfusion therapy, and the role of the spleen. Transfusion and chelation therapies represent significant advancements in disease management. Indeed, they have greatly improved the prognosis of thalassemia and SCD, as evidenced by epidemiological data [17]. However, the benefits of allogenic blood transfusions (ABTs) are accompanied by the drawbacks of a high transfusion burden, leading to direct exposure to infectious risks and indirectly contributing to transfusion-related immunomodulation (TRIM) and iron overload. Other therapeutic interventions such as splenectomy, central venous catheters, bone marrow transplantation, or nutritional deficiencies (e.g., zinc deficiency) further elevate the risk of infections [18].

In thalassemia patients, infections rank as the second leading cause of death following cardiac issues, primarily due to iron overload. Various factors contribute to increased infection rates in these patients, including thalassemia, immunological abnormalities, blood transfusions, iron overload, chelation therapy, hematopoietic stem cell transplantation, nutritional deficiencies, and splenectomy [19]. Iron overload leads to complications such as endocrinopathy, cardiomyopathy, and

dysfunction in other organs [19]. In resource-constrained settings, administering iron chelators alongside blood transfusions is a common treatment approach for major thalassemia patients [20]. Previous research has shown that iron chelators can enhance the immune system and neutrophils' phagocytic function while reducing iron overload. Consequently, abnormal immune function and an increased susceptibility to infections may be linked to iron overload in patients with thalassemia major [21, 22].

The current study aimed to follow up on some blood and immune indicators in thalassemia patients infected with the *Giardia lamblia* parasite.

Materials and Methods

This experimental study was conducted at the Thalassemia Center in Thi-Qar province, Iraq, in 2022**.** Seventy individuals, including 50 patients and 20 healthy controls, were selected by accessible sampling. Patients were composed of three groups. The first group involved twenty-five thalassemic individuals who had giardiasis. The other 14 individuals (the second group) were thalassemic and were giardia infection-free. They were among the patients diagnosed with beta-thalassemia who were registered at the Thalassemia Center in Thi-Qar province-Iraq, and the remaining 11 patients (third group) were free of thalassemia but had a giardia infection. The study also involved 20 healthy individuals selected as a control group.

Disposable syringes were split into two parts to extract five millimeters of fasting blood. The first was moved to a plain tube filled with ethylene diamine tetraacetic acid disodium (EDTA) to measure hemoglobin using a hematology analyzer (Genex, Count60; USA). White blood cell count and neutrophil activity could also be measured using Nitroblue Tetrazolium stain. The second portion was put into a basic polyethylene tube containing gel, which functioned as a substance that triggers clot formation during serum separation. The sample was centrifuged using a Hermle Z-200-A centrifuge from Germany at 4000 revolutions per minute for 10 minutes. Subsequently, the resulting serum was promptly distributed into four Eppendorf tubes, each appropriately marked.

The levels of interleukin-6 were measured in the serum employing an enzyme-linked immunosorbent assay (ELISA). Using the spectrophotometer APEL PD-303/Japan, the iron levels were measured by Randox/England, ferritin by BioMeriux/France, and transferrin by LTA/Italy.

The SPSS 20 statistical program was used to perform the statistical analysis. Analysis of variance (ANOVA) was used to determine whether there were any notable differences in the group means in the data. The differences between the means of the groups were evaluated using the least significant difference at a significance level of $p<0.01$.

Findings

The study enrolled 50 patients of both sexes (21 males and 29 females), ranging in age from 2 to 15 years, and 20 healthy children of the same age who were selected as a control group.

The average number of white blood cells (mm^3) was significantly higher ($p<0.001$) in thalassemic patients, specifically those with giardia, when compared to the control group. This can be attributed to the patients' heightened susceptibility to infections. Conversely, the mean number of neutrophils diminished significantly ($p<0.001$) compared to the control group. Regarding interleukin-6 (IL-6), crucial to the pathophysiology of thalassemia, the findings showed that infections caused patients' concentrations of IL-6 to rise significantly (Table 1).

Compared to the control group, the patient groups had substantially greater iron and ferritin levels but much lower transferrin levels (Table 2).

Table 1. IL-6 concentrations, WBC counts, and neutrophil activity mean in the blood of thalamic and giardia patients and the control group

Parameter	Thalassemia	Giardia	Thalassemia with giardia	Control	p-Value
IL-6	28.20±8.05	23.29±7.06	30.94±9.95	16.09±4.10	<0.001
WBCs	9949.0±19.0	7988.0±17.2	11986.0±13.4	6531.0±13.8	<0.001
Neutrophil Activity	9.21±0.68	13.33±3.01	10.43±1.20	19.20±9.70	<0.001

Table 2. Mean iron study in the serum of thalassemic and giardia patients and control groups

Parameter	Thalassemia	Giardia	Thalassemia with giardia	Control	p-Value
Iron (mg/dl)	119.90±32.33	101.29 ±3.10	200.13±19.71	70.38±14.90	<0.001
Transferrin (mg/dl)	218.09±17.02	192.67±17.44	186.13±28.33	410.81±29.19	<0.001
Ferritin (ng/dl)	4413.18±77.32	5044.15 ±10.99	6018.19±20.33	123.75±29.99	<0.001

Discussion

The current study aimed to follow up on some blood and immune indicators in thalassemia patients infected with the *Giardia lamblia* parasite. Both hemoglobin and myoglobin rely on iron as an essential component. Heme iron and non-heme iron are the two accessible types of dietary iron. Ferritin stores iron, is released from hemoglobin, and is linked with transferrin before being transported to the bone marrow for new hemoglobin production. Periodic blood transfusions, often used to treat thalassemia, may cause a buildup of acquired iron excess in the body [23-27].

It is well known that a blood transfusion provides the body with around 250mg of iron. However, the body can only discard up to 1mg of daily iron added to its

stores [28, 29]. The serum ferritin levels of patients with cirrhosis of the liver are higher. Nevertheless, similar to primary iron overload, the principal factor leading to illness and mortality is ultimately the progressive failure of the liver and heart [28]. Inflammation, from infections to chronic diseases, raises serum ferritin protein. To determine the cause of high serum ferritin, serum iron, and transferrin must be measured [30]. Compared to transferrin, iron has a much shorter half-life in plasma, which causes momentary variations [31]. Thus, the higher levels of transferrin and ferritin, compared to the control group, and the increased serum iron suggest an excess in the afflicted individuals.

When serum ferritin levels are significantly elevated, regardless of the underlying cause, it raises concerns, prompting a more aggressive iron chelation therapy approach. Serum ferritin typically decreases as iron stores decrease, except in cases where inflammation elevates ferritin levels due to its role as an acute phase reactant. In a study conducted by Bandyopadhyay et al., even younger patients exhibited high serum ferritin levels. For instance, in the 1-5 age group, the average serum ferritin was 1750 ng/ml, which increased to 3650 ng/ml in patients aged 11-15 [32]. However, controlling serum ferritin levels proved challenging, as only a few patients fully adhered to the recommended regimen at home [33].

A small portion of ferritin, which is in equilibrium with the body's iron stores, circulates in the plasma. Elevated plasma ferritin levels indicate excess iron stores, while decreased levels suggest iron deficiency [34, 35]. However, quantifying serum ferritin using antibodies to ferritin protein does not directly reflect the iron content of ferritin. Serum ferritin protein serves as an acute phase reactant, and apoferritin (a form of ferritin protein with minimal iron content, not in equilibrium with body stores) levels rise during inflammatory conditions such as infection [36], rheumatoid arthritis [37], hepatitis [38], and cancer [39]. This elevation is partly due to interleukin 1 stimulating the translation of apoferritin mRNA [40]. Therefore, when assessing iron status, both transferrin-bound iron and transferrin saturation should be measured in the same serum sample alongside ferritin protein to differentiate between iron levels and inflammation. Just as elevated serum ferritin protein levels may indicate inflammation rather than iron overload, low serum iron levels may suggest inflammation rather than iron deficiency. An accurate assessment of iron status can only be made when both serum iron and serum ferritin protein levels change in the same direction (i.e., both increase or decrease).

Measuring serum ferritin protein levels is widely accepted as the most effective noninvasive method for assessing body iron stores. Still, it's crucial to consider both serum ferritin protein and serum iron levels concurrently. Elevated serum ferritin protein levels can occur without a corresponding increase in iron stores, especially in acute inflammatory conditions or in cases of liver disease or cancer [41-43], where serum ferritin protein levels typically exceed 400ng/ml. While serum ferritin protein levels above 400 ng/ml often indicate iron overload in clinical practice, this interpretation should be confirmed by assessing transferrin's percentage of iron saturation (iron BC). Consistent with our findings, Herbert *et al.* [44] demonstrated that serum ferritin iron levels effectively differentiated individuals with homozygous hemochromatosis from those with elevated ferritin due to inflammation. Additionally, the percentage of ferritin protein saturation with iron reliably distinguished individuals with high body iron from those experiencing inflammation.

Conclusion

The thalassemia and giardia patients have greater iron and ferritin levels but much lower transferrin levels than the healthy individuals.

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