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A STUDY OF THE PREVALENCE OF LEISHMANIASIS IN KIRKUK GOVERNORATE AND EVALUATION OF SOME IMMUNOLOGICAL AND BIOCHEMICAL INDICATORS IN LEISHMANIASIS PATIENTS

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Abstract
The current study was conducted on cases of Cutaneous Leishmaniasis Cutaneous infected with cutaneous Leishmaniasis that were received in hospitals in Kirkuk Governorate for the period from 1/7/2022 to 1/7/2023 retrospectively. 800 smears of skin lesions were examined under a compound microscope after being stained with Leishmaniasis stain or part of it was transplanted into the medium. Al Zarai (NNN) (Novy-MacNeal-Nicolle) at 23 C°. The results of the study showed that all samples were infected with a higher risk of infection by 40.92%, of which 25.6% were females and 15.75% were males. 45% infection rate.
Also The study included the evaluation of immunological and some biochemical indicators in patients with Leishmaniasis Cutaneous. The current study included the collection of 100 blood samples from patients with Leishmaniasis Cutaneous whose ages ranged between (1-60) years for the period from 1/2/2023 to 1/5/2023. From the Oncology Hospital of the Medical City in Kirkuk Governorate the samples were divided into two groups: The first group (G1) which involve 60 samples from Leishmaniasis Cutaneous and 30 samples of healthy people.
-The study included estimation of the levels of (Interferon-γ، Tumor necrosis factor ، IL-10، Iron) and liver function which include (AST،ALT) for the samples under study.
The results obtained from the current study:
- The INF-γ, TNF-α, IL-10 level significantly elevated (P≤0.05) in the serum of G1 compared to healthy group.
-The liver function activity enzyme significantly elevated (P≤0.05) in the serum of G1 compared to the healthy.
-The Iron level significantly decrease (P≤0.05) in the serum of G1 compared to the healthy group.

Keywords: Leishmaniasis Cutaneous , , Interferon-γ ,Tumor necrosis factor , Interlukine-10 , Liver Function.

Introduction

Leishmaniasissis is a parasitic disease transmitted by a vector, and it is through the sting of a female sand fly, which causes differenttypes of leishmaniasissis, which manifests itself in three main clinical forms: Cutaneous Leishmaniasissis, Mucocutaneous [1,2]
Leishmaniasissis is considered a disease of high importance, and its distribution rates differ from one country to another [3], as it is a public health problem in tropical and subtropical regions , Cutaneous leishmaniasissis is a very old disease in Iraq, called Bagdad Boil, and it is the least

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severe form represented by the appearance of sores that are characterized by self-healing, and Leishmaniasis major and Leishmaniasis tropica are the causative agents of cutaneous leishmaniasissis in Iraq 2009 (Alavinia according to species). Parasites and the immune response of patients, and different symptoms in the areas, the infection begins in the form of erythematous papules, increasing in size to produce nodules, ulcers and crusts Control [4].

Interferon-gamma is a type of cytokine with a molecular weight of 34 kDa. Type I lymphocytes—CD4+ T helper cells, CD8+, cytotoxic lymphocytes, and NK cells—Nature Kills—was thought to exclusively produce interferon-gamma, however, research indicates Recent studies indicate that other cells such as B cells, natural killer cells, dendritic cells, and macrophages also secrete interferon-gamma [5].

Tumor necrosis factor alpha-TNF-α is a cytokine that is secreted from macrophages, killer cells, and T cells. This cytokine works to promote inflammation and activate the lining of blood vessels [6], as it is an angiogenesis factor that stimulates them by promoting endothelial cells to divide and influence elements Pro-angiogenesis [7]. It is considered one of the cytokines that have an important role in stimulating reactions in the advanced stages of inflammation including cytokines (IL-1β, IL-6, TNF-α, IL-17), chemokines, and autoantibodies that lead to an exacerbated activation of immune system cells (8), and it is produced by many cells, including CD4 lymphocytes, killer cells, and nerve cells in acute infections, and it is responsible for triggering signals within cells, which leads to Necrosis or cell death and antibodies are produced by stimulating B-lymphocytes (B-cells); known as IgM, IgG, IgA and IgE. These antibodies are functionally acting on the eradication of the infection and removing the parasite found free in body fluids by activation of supplement pathways and catalytic activity of immune system (9).

Material and Methods

The study included the collection of skin biopsies from 800 clinically diagnosed cutaneous leishmaniasissis of both sexes and different age groups who had not previously undergone treatment. Information was obtained from all participants regarding name, age, gender, address, and a record of the number and location of ulcers. A swab was taken from the edge of the strong lesion [10]. The samples were placed on glass slides, stained with Leishman's dye, and examined with a compound microscope [11].

How to transplant the parasite:

After sterilizing the lesion area with ethyl alcohol, a biopsy was taken from the strong edge of the ulcer and placed directly on the culture medium (NNN) previously prepared and prepared under sterile conditions. The culture medium consists of a biphasic medium of the solid phase, which was prepared using the [12] method, and the liquid phase (lock solution), which was prepared using the [11] method. The culture was incubated at 23 °C for one month and examined every four days by microscope. compound to monitor parasite growth.

Study Samples: The study was conducted on (100) blood samples were collected during the period from 1/2/2023 to 1/5/2023. From the Oncology Hospital of the Medical City in Kirkuk Governorate , and were divided into two groups: (G1) which involve 60 samples from patients with Leishmaniasis Cutaneous and 30 samples of healthy women as a control

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group (C).

Collection of blood samples and preparation:

Were taken serum (5) ml of the drawn blood and put it in a plastic tube with a tight-fitting lid and free of anticoagulant (Plain tube) left at room temperature until the blood coagulates and then put in a centrifuge at a speed of (4000) rpm for (15) minutes The blood serum was kept at a temperature of (-20) C until use and biochemical analyses. The blood samples were transferred in a cool box to the laboratory for testing.

Determination of cytokines level in serum

The (INF-γ ,TNF-α, interleukin-10) level was estimated according to the kit prepared from the Chinese company Melsin and using the ELISA technique using the double ELISA sandwich method for antibodies.

Determination of Iron level in serum

The iron concentration was calculated using the colorimetric method that converts trivalent iron to iron(II) in a weak acid medium, and it forms a colored complex of the iron(II) ion with (13).

Determination of Liver Function in blood serum

The liver enzymes was estimated by using a kit LiNEAR prepared from the Spanish company, the researcher's method [14].

Statistical analysis:

The SPSS statistical program was used to find the Mean ± (SD), as the special differences between the patient and the healthy group were determined by using (T. Test) to show the difference between patients and heathy subject ($P \leq 0.05$).

Results and Discussion:

Distribution of cutaneous leishmaniasissis cases:

By gender:

The results in table (1) showed that the total incidence rate in males was 56.25% distributed among different age groups, where the highest rate was diagnosed in the age group 1-10 years, when it was 25.6%, and the lowest was in the age group 51-61 years, when it was 2.5%.

Table(1):-Showed Distribution of cutaneous leishmaniasissis cases

Percentage	Total	Sex				Gender
		Percentage	Female	Percentage	male	
41.37	331	15.75	126	25.6	205	10-1
26.87	215	11.87	95	15	120	20-11
19.75	158	10.12	81	9.62	77	30-21
5.75	46	3.25	26	3.5	28	40-31
6.25	50	2.75	22	2.5	20	60-51
100	800	43.75	350	56.25	450	

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Distribution of cutaneous leishmaniasissis cases by depending on the type of ulcer

The results in table (2) showed that there was a significant difference in the type of ulcer, as the number of dry sores was 550, or 86.75%, and the number of wet sores was 250, or 31.25%. The percentage of dry sores in males was higher than that of females, amounting to 43.75%, while the wet sores were higher in females by 18 than males. .75%.

Table (2):- Showed Distribution of cutaneous leishmaniasissis cases by depending on the type of ulcer

Percentage	Total	Sex				Gender
		Percentage	Female	Percentage	male	
68.75	550	25	200	43.75	350	Dry
31.25	250	18.75	150	12.5	100	Moist
100	800	43.75	350	56.25	450	Total

Fig(2):- children with Moist cutaneous leishmaniasissi

Fig(1):- male with dry cutaneous leishmaniasissis

Distribution of cutaneous leishmaniasissis cases by the number of canker sores

The results in table (3) showed that there was a significant difference for patients infected with Leishmaniasis parasite, as the highest percentage was 45% for those with one ulcer, 27.5% for two ulcers, and the lowest percentage was 0.5% for the number of ulcers9. The rest of the ratios were distributed between the two previous ratios.

Table (3):- Showed Distribution of cutaneous leishmaniasissis cases by the number of canker sores

Percentage	Infected	N. of ulcers
45	360	1
27.5	220	2
12.12	97	3
6.87	55	4
3.75	30	5
1.87	15	6
1.25	10	7
1.12	9	8
0.5	4	9

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Estimation of Immunological and biochemical variables for the samples under study:

Table (4): shows the mean ±S.D of the Immunological and biochemical variables of the samples under study

Groups / Parameter	Mean ± SD Control n=60	Patients n=30	P-Value
INF-γ (Pg/ml)	19.44 ± 5.11	36.12 ± 12.09	P ≤ 0.05
TNF- α (Pg/ml)	24.11 ± 5.22	50.01 ± 13.28	P ≤ 0.05
IL-10 (Pg/ml)	.0408 ± 0.208	.0978 ± 0.114	P ≤ 0.05
Iron (µgm/dl)	150.04 ± 14.91	118.13 ± 22.04	P ≤ 0.05
AST (IU/L)	18.72 ± 2.11	30.91 ± 4.19	P ≤ 0.05
ALT(IU/L)	20.37 ± 3.13	28.20 ± 4.20	P ≤ 0.05

Significant P ≤ 0.05

The results of the current research showed a significant rise at (p ≤ 0.05) in (INF-γ, TNF-α, IL-10, AST, ALT) level and a significant reduction in Iron in serum of patients with Leishmaniasissis compared to healthy subject. as in Figures (3,4,5,6,7,8) respectively.

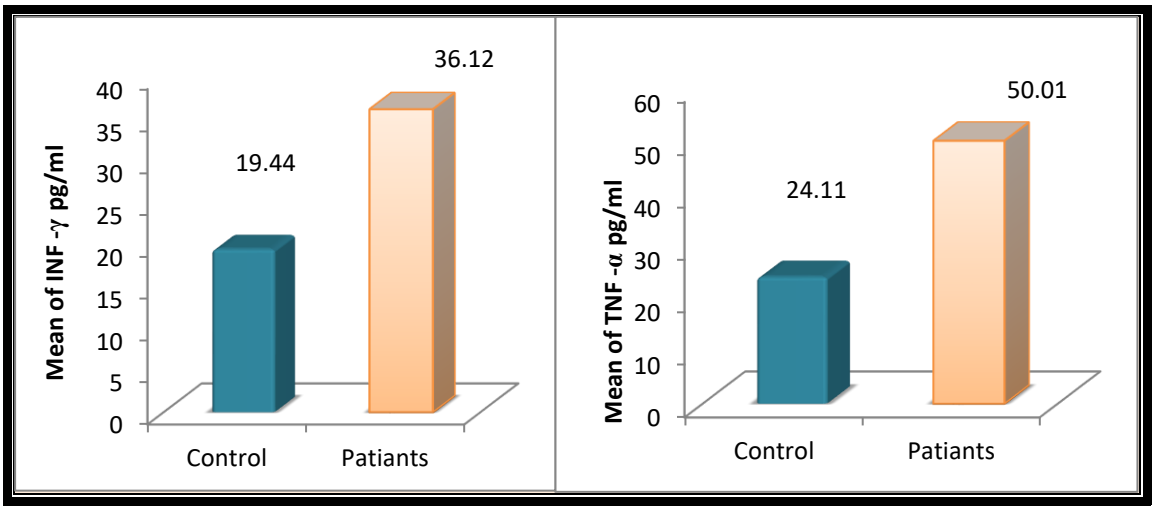

Figure 4: TNF-α in the serum of the two group

Figure 3: INF-γ in the serum of the two group

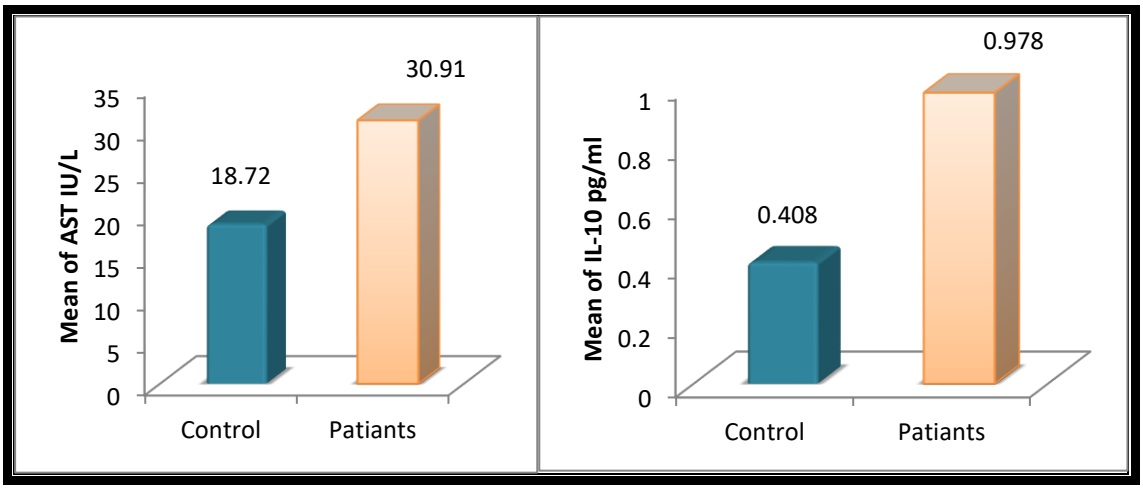

Figure 5: IL-10 in the serum of the two group

Figure 6: AST in the serum of the two group

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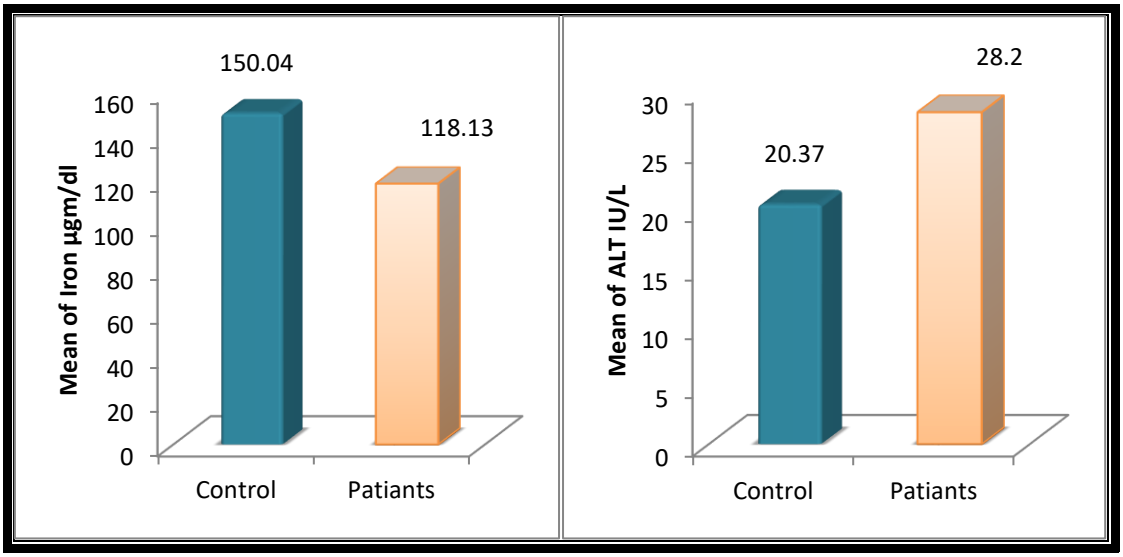

Figure 7: ALT in the serum of the two group Figure 8: Iron in the serum of the two group

Discussion

The results of this study were consistent with the results of the aforementioned studies in various Iraqi governorates, as these studies showed that the incidence of cutaneous Leishmaniasis is most often in the age group of less than three years [15,16,17,18,19].

Pringle (1957)[20] also showed that cutaneous Leishmaniasis is common in children under the age of 12 years in endemic areas, as well as the World Health Organization [21] WHO, which indicated in its report that children under the age of twelve are more susceptible than others to infection with this disease. from the areas in which they live. As for Tarish [22] in the province of Najaf, he noted the prevalence of infection in the age group of (5-24 years) more than others, as well as Al-Janabi [23] in the province of Babylon, he noted that most of the cases of infection were in the age group less than 10- 15 years . Al-Tufaili (2003)[24] in Al-Najaf Governorate also found that the highest infections were in the age group 5-24 years, while Mahmood (2006)[25] found in Hawija district, Kirkuk governorate, that most of the injuries were in the age group of more than 15 years. Dahham and Al-Alusi [17] concluded Also, the age group less than 6 months 10 years recorded an infection rate of 59.62%. Rahi [18] also recorded in Iraq an infection rate in the age group 0-6 years, amounting to 43.2%, followed by the age group 7-12 years, and the age group 18-135, as it reached 18.2%, and finally the age group is greater or equal to 19 years It reached 9% for both sexes, which is consistent with the results of the current study, as the incidence decreases with increasing age group. In Diwaniyah governorate, Al-Mayali [15], Kashkul [16] and Al-Daffi [19] noted that the age group of (10) (years) is the most affected in this governorate.

The results of the current study agreed Salman (2017)[26] in Najaf, so the percentage of dry ulcers was higher, by 76.47%, and wet ulcers by 11.76%. It also agreed with Al-Musawi (2015)[27] in Dhi Qar Governorate, where the highest infection rate was recorded in dry ulcers, 72.1%, and the lowest percentage was in ulcerated ulcers, and the least wet, 14% while the current results did not agree with Samarai & Al-Obaidi,(2009)[28] as the percentage of wet ulcers was 63.5% and the percentage of dry ulcers was 36.5 and the study of Al-Shukr (2012)[29] In Al-Najaf, as the percentage of wet ulcers was higher at 51.21% compared to dry ulcers 15.85 And the results of

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Al-Hany (2014)[30], where the percentage of wet ulcers was higher than that of dry ulcers, by 60% and 40%, respectively, and the results of Rahi et al (2014)[31], in Kut governorate, where the percentage of wet ulcers was 61%, while dry ulcers 39 %, and the results of Al-Mousawi (2015)[32] in the central and southern governorates, where the percentage of wet ulcers was 7955% and dry ulcers 20.44%.

Results agreed The current study With Some studies [33,34,35], reported that most patients had one ulcer, as agreed with the Al-Hassani study[36], which recorded a rate of 47.5% for single ulcers and 229% for multiple ulcers. of ulcers, while it did not agree with AL-Saady (2014)[37] when it recorded the existence of 43 cases with multiple ulcers compared to 41 cases of single ulcers as well. Study Ali [38] in Najaf, where it recorded 75% for single ulcers and 25% for multiple ulcers; The reason for this is due to the long periods of exposure to repeated and successive pricking by sandflies, and the high density of sandflies in this region plays an important role in that [39]. Whereas Al-Qadhi [40], indicated that the reason is due to the optimal conditions that allow recurrence of infection, such as the nature of the area exposed to pricking, the abundance of sandflies, and the nature of the immune response of the individual.

Leishmaniasis is a global disease endemic in many countries, including Iraq, as a feature of Leishmaniasis is the development of skin ulcers that are controlled by the immune system. An elevated level of inflammatory cytokines can affect this parasite [41]. And the high level of INF-γ in the group of patients confirms this, as the results of our current study agree with the results of (Sahu) [42] , Aladdin [43], who indicated in their study that there were early efforts to reduce the proliferation of parasites Which was represented by the increase of interferon-gamma during the early stages of infection with the Leishmaniasis parasite, compared with the control group. The reason for the rise is due to the stimulation of the innate immune response and the occurrence of modification of the overproduction of cytokinesis by T lymphocytes. Therefore, the reason for the high concentration of cytokinesis may be due to the presence of a large number of macrophages, lymphocytes, and epidermal cells present in cutaneous Leishmaniasis ulcers [44]. Cytokinesis activates CD4+ and CD8+ as it links the immune response and pathogenesis. And the level of INF-γ rises with the increase in the number of ulcers as a result of the frequency of T-cell and CD8+ cells with the intensity of the inflammatory reaction that increases with the increase in the number of ulcers and works to kill the Leishmaniasis parasite. As the exaggerated inflammatory response of cutaneous Leishmaniasis s due to the parasite's continued stimulation of the immune system as a result of the decrease in the ability of regulatory cellular movements for the purpose of modifying the inflammatory response [45].

Elevated values of cytokinesis in patients with Leishmaniasis cutaneous who have multiple ulcers of wet type due to the high number of macrophages, lymphocytes and epidermal cells present in the lesion. It stimulates the effect of T cells during infection with cutaneous Leishmaniasis, whereby infection with cutaneous Leishmaniasis causes an immune response, INF -γ inhibits the production of IL-10 and is associated with the Th2 response, INF-γ works to induce a protective immune response against disease and prevent its spread [44].

In addition, TNF-α showed a significant increase in the serum of patients with Leishmaniasis parasite compared with the control group, as the current results agree with the findings of Hussein and his group [46] and (Taher) [47], who confirmed in their study the increase The observed TNF level may give an important insight into this anti-inflammatory cytokine as a biomarker in the

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diagnosis and tracking of disease progression.

TNF-α is produced by macrophages in tissues when infection with Leishmaniasis parasite occurs, and activates T cells to produce inflammatory kinetics and works to kill Leishmaniasis parasite along with other kinetics. The high concentration of cytokinesis causes a large number of macrophages and lymphocytes present in cutaneous Leishmaniasis ulcers. TNF-α activates phagocytic cells and mediates cytokinesis response, thus limiting tissue damage [(44)]. The variation in the level of this cytokinesis is due to the identification of parasite antigens at the beginning of infection by the regulatory T-cell cells, and these cells promote the inflammatory response and the high level of cytokinesis TNF-α, then an innate immune response occurs due to the presence of inflammatory monocytes whose numbers increase in Leishmaniasis Cutaneous skin, which is a source of TNF-α The production of TNF-α cytokinesis depends on the activation of CD4 and CD8+ The production of TNF-α exacerbates with an increase in the number of ulcers due to the frequency of T-cell and CD8+ cells The production of TNF-α exacerbates with the severity of the inflammatory reaction that increases with an increase in the number of ulcers and works to kill parasite. As the exaggerated inflammatory response in cutaneous Leishmaniasis is due to the parasite's continued stimulation of the immune system as a result of the decrease in the ability of regulatory cellular movements to modify the inflammatory response [(45)].

In addition, IL-10 showed a significant increase in the serum of patients infected with Leishmaniasis parasite compared with the control group, as the results of the current study agree with the results of Silva [(48)] , Mohamed [(49)], who indicated the association of interleukin-10 with the development of disease Leishmaniasis because it inhibits the effect of connective Leishmaniasis and the production of inflammatory mediators, including INF-γ. Therefore, there is a relationship between the development of the disease and interleukin-10. IL-10 controls the development of the disease, as the inflammatory infiltration occurs from Leishmaniasis cutaneous ulcers and consists of T cells and B cells, either natural killer cells are few or non existent, It contributes to the expression of IL-10 in the lesion, and T cells are important in the production of inflammatory IL-10, which is produced by T cells to stimulate cellular response, and works to kill the Leishmaniasis parasite with other cytokinesis and stimulates the production of nitric oxide, which works on tissue damage [(50)]. Elevation of IL-10 correlates with the severity of infection, as it is a pro-inflammatory kinetics, and its decrease indicates an exacerbation of the inflammatory immune response. IL-10 is produced by CD4+ and CD5+ and maintains immunity against Leishmaniasis after recovery and the balance between cellular kinetics to maintain a protective reaction against adaptive immunity [(51)].

As for iron, it showed a significant decrease in the serum of a group of patients with Leishmaniasis, compared with the control group, as the results of the current study agree with the results of Al-Hassani [(52)] , Dighal [(53)], and the reason for these changes is attributed to a part of strategies The defense of living organisms under which factors such as: IL-1, TNF-a, and IL-10 [(54)], and the role of iron in the interaction between parasites and the host is one of the main steps in the interaction between the host and infection as it works on the reproduction of the parasite inside the cell and increases its number and dissemination, and the parasites need to obtain nutrients from the host to support its growth and to compete with the host to limit its availability of nutrients [(55)]. Thus, pathogens have developed various sophisticated mechanisms to compete with the host for its

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nutrients, and iron is one of the important micronutrients for the host and parasite that mediates host-pathogen interactions. depleted iron intake and reduced iron absorption [56].

In addition, the liver function represented by (AST, ALT) showed a significant increase in the serum of patients infected with Leishmaniasis parasite compared with the control group, as the results of the current study agree with the results of the study of Younis [57] and Endale [58] who showed an rise Significantly in liver enzyme among infected with the leishmaniasis parasite, and the reason for this is attributed to liver injury, as changes in liver enzymes lead to liver damage or a change in the flow of bile, and thus the enzyme is released when liver cells are damaged [59].

AST or ALT levels are primarily a valuable aid in diagnosing liver disease. Although not specific for liver disease, it can be used with other enzymes to monitor the course of various liver disorders. Normal concentrations in the blood are 5 to 40 U/L for AST and 5 to 35 U/L for ALT. However, when body tissues or an organ such as the liver or heart are injured or damaged, more AST and ALT are released into the bloodstream, causing their blood levels to rise. Levels of these enzymes can rise from 10 to 20 times greater than normal. Therefore, the amount of AST and ALT in the blood is directly related to the extent of tissue damage [60].

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