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Assessment of Interleukin-10 Levels in Iraqi Diabetic Type 2 Patients Infected with Toxoplasmosis

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Abstract

Background: Toxoplasmosis is a disease caused by an obligate intracellular protozoan parasite *Toxoplasma gondii* that infects birds and mammals as an intermediate host while infecting cats as a definitive host. Diabetes mellitus is a global metabolic disorder that appeared due to inappropriate hyperglycemia. Interleukin-10 is an immunoregulatory cytokine that plays a main role in modulating inflammation, it's considered as main inhibitory cytokine against the action of inflammatory cytokines such as IL-12. The main aim of this study is to assess the levels of IL-10 in Iraqi diabetic type 2 infected with toxoplasmosis.

Methods: This study concluded 109 cases of Iraqi diabetic type 2 patients and 80 samples of healthy individuals collected from private lab in Baghdad, Iraq, during period from March to June 2022 with age mean 49.9 ± 1.29.

Results: The results showed that the group of diabetes has the highest level of glucose in diabetes diagnostic tests 7.9 ± 0.178 HbA1C, 174.55 ± 3.96 mg/dl FBS and 216.89 ± 4.96 mg/dl RBS respectively. Moreover, 51/109 samples of diabetic patients have highest level of IgG anti-*Toxoplasma* 34.95 ± 7.5 UI/mL in CMIA followed by 30/80 samples of healthy individuals have seropositive for the same antibody 32.7 ± 8.45 UI/mL in the same assay with significant differences While, all samples were seronegative for IgM anti-*Toxoplasma*. The group of healthy control has the highest levels of IL-10 in ELISA 320.43 ± 17.64 pg/ml followed by the group of diabetic patients 138.38 ± 5.69 pg/ml. Also, the concentration of this interleukin was in the group of toxoplasmosis patients which considered as a control positive 115.45 ± 4.44 pg/ml. While, the group of diabetic patients with toxoplasmosis has the lowest concentration of the interleukin 102.3 ± 7.05 pg/ml with highly significant differences.

Conclusion: The conclusion of this study is the IL-10 has been shown highest levels in healthy control in comparison with other study groups.

Introduction

Toxoplasmosis is a widespread parasitic zoonotic disease caused by *Toxoplasma gondii* and occurs worldwide. It has a worldwide distribution and is one of the most widespread sources of infection in Iraq. *T. gondii* is an obligate intracellular protozoan parasite that infects almost all warm-blooded animals, with mammals such as birds and humans serving as intermediate hosts. The final host of this parasite is the cat [1, 2]. Infection occurs mainly by eating food and drinking water contaminated with *T. gondii* oocysts or tissue cysts. Toxoplasmosis is an infectious disease of widespread concern, but the disease has no unique clinical manifestations. *T. gondii* is an opportunistic parasite that infects immunocompromised individuals [3-5].

This parasite efficiently spreads to all organs of the body due to its ability to escape into macrophages and dendritic cells. Eventually, immune compression against the parasite leads to the formation of cysts containing slow-growing bradyzoites [3]. Toxoplasmosis can cause fetal death if the parasite is transmitted through the placenta (transplacentally) or during vaginal delivery from an infected mother [6].

Diabetes mellitus (DM) is a syndrome caused by abnormal metabolism accompanied by inappropriate hyperglycemia due to an absolute deficiency of insulin secretion or decreased bioavailability of insulin, or both. Diabetic patients are prone to develop systemic microangiopathy, atherosclerosis, and neuropathy. Currently, the number of cases of this disease is increasing in developed countries around the world, which can adversely affect the quality of life of people with diabetes, making it a global disease problem [7, 8]. It is now very clear that diabetes is one of the chronic non-communicable diseases that can affect the entire world population in both developed and non-developed countries [9]. Diabetes is mainly classified into one of her two types: T1DM refers to insulin-dependent diabetes mellitus and T2DM refers to non-insulin dependent diabetes mellitus. T2DM is characterized by abnormally high blood sugar levels caused by a relative deficiency of insulin [10, 11].

T. gondii can infect nucleated cells such as pancreatic cells, causing β-cell destruction and insulin secretion. In addition, the risk of acute and chronic pancreatitis and diabetes is also increased [12]. Bradyzoites have been identified in tissue cysts, bile duct epithelial cells, and acinar cells of pancreatic tissue [13, 14]. However, T2DM is thought to be a chronic inflammatory disease that causes multiple alterations in immune cell function [15, 16, 17]. *T. gondii* induces one of the most potent innate proinflammatory responses of any infectious agent. In addition, it manipulates immune responses specific to immunization against *T. gondii*. A delicate balance exists between parasite and host, including a chain of formatted cellular interactions involving enterocytes, dendritic cells, neutrophils, natural killer cells and macrophages [18, 19].

The anti-inflammatory cytokine IL-10 plays an important role in limiting the detrimental pathological effects of the inflammatory response in toxoplasmosis. This cytokine is secreted by macrophages, dendritic cells, B cells, Th2 cells, and regulatory T cells [20]. Suppression of the T cell-dependent immune system by IL-10 is primarily aimed at preventing overwhelming inflammation that ultimately leads to death. In addition, IL-10 inactivates macrophages and IFN-gamma strongly stimulates *Toxoplasma* acidity, promoting parasite intracellular survival. Consequently, IL-10 stimulates her *T. gondii* post-infection suppression, is beneficial to both parasite and host, and promotes a consistent host-parasite relationship [21].

The aim of this study is to find the role of IL-10 and assess its levels in Iraqi diabetic type 2 patients infected with toxoplasmosis in comparison with other studied groups.

Methods

Subjects and Samples

The current study included 189 cases, divided into two groups according to diabetic infection. 109 samples from Iraqi type 2 diabetic patients who were diagnosed by experts and participated in diabetes testing at private laboratories in Baghdad, Iraq between March and June 2022. Eighty Iraqi specimens collected from non-diabetic patients during the period were compared by age. The age range of all cases is 15 to 85 (49.9 ± 1.29). Five ml of venous blood was drawn from each sample. Serum was then separated in gel tubes and used for diabetes, toxoplasmosis assays, and IL-10 concentration measurements.

Diabetes mellitus diagnosis

Blood glucose measurement by fasting test followed by random testing using the Glucose Architect Kit (Abbott GmbH, Germany) and measurement of glycated hemoglobin levels using the Hemoglobin A1C Architect Kit (Abbott GmbH, Germany) according to the manufacturer's instructions.

T. gondii diagnosis

Toxoplasma antibody IgM and IgG Chemiluminescent Microparticle Immunoassay (CMIA) Architect Toxo IgM/G Kit (Abbott GmbH, Germany) was used to detect *T. gondii* according to the manufacturer's instructions.

Assessment IL-10 levels

IL-10 (interleukin 10) levels were measured via using a sandwich enzyme-linked immunosorbent assay (ELISA)

kit for human IL-10 (mybiosource Inc., USA) according to the manufacturer's protocol.

Statistical Analysis

The statistical analysis system (22) was used in this study. A program that assesses the impact of various factors on research parameters. A least significant difference (LCD) test, also known as analysis of variance (ANOVA), was used to make meaningful comparisons between means. The study used a chi-square test to make a significant comparison between percentages with probabilities 0.05 and 0.01.

Results

Diabetes mellitus diagnosis

Table (1) demonstrated that the diabetic group had the highest blood glucose levels on all diabetic tests compared to the healthy control group and the fasting test showed a significant difference ($P \leqslant 0.05$), whereas the fasting test showed a significant difference ($P \leqslant 0.05$). The test shows a highly significant difference ($P \leqslant 0.01$) in random test and glycated hemoglobin test.

T. gondii diagnosis

According to the chemiluminescent microparticle immunoassay revealed in table (2), 51/109 of diabetic patients had the highest anti-*Toxoplasma* IgG level at 34.95 ± 7.5 UI/ml followed by 30/80 of non-diabetic controls at 32.7 ± 8.45 UI/ml with significant difference, the study groups were divided into the following four groups according to their anti-*Toxoplasma* IgG values. diabetic patients infected with toxoplasmosis, diabetic patients only, non-diabetic individuals infected with toxoplasmosis considered as a positive control and healthy individuals are considered as a negative control. However, all samples from diabetic and non-diabetic controls were seronegative for anti-*Toxoplasma* IgM and were significantly different.

Assessment of IL-10

Thirty samples of each group used in sandwich ELISA to determine the levels of IL-10 which demonstrated in table (3) that healthy control has the highest level of IL-10, whereas the group of diabetic patients with toxoplasmosis has the lowest level of interleukin with

Groups	Total No. of samples for each group	Mean ± SE of HbA1C (Glycated Hemoglobin)	Upper Value	Lower Value	Mean ± SE of FBS mg/dl (Fasting blood sugar)	Upper Value	Lower Value	Mean ± SE of RBS mg/dl (Random blood sugar)	Upper Value	Lower Value
Diabetic Patients	109	7.9 ± 0.178	15.5	5.3	174.55 ± 3.96	300	120	216.89 ± 4.96	410	125
Non-Diabetic Control	80	4.98 ± 0.044	5.4	4.3	96.65 ± 0.749	98	81	160.25 ± 2.69	195	109
LSD value		1.667 *			26.381 **			31.093 **		
P-value		0.0252			0.0063			0.0058		
Significant * (P≤0.05), Highly significant ** (P≤0.01).										
Reference range of HbA1C Normal < 5.7 Prediabetes 5.7 – 6.4 Diabetes ⩾ 6.5.		**Reference range of FBS** Normal < 100 mg/dl. Prediabetes 101 – 125 mg/dl. Diabetes ⩾ 126.								
Reference range of RBS: over 200 mg/dl after two hours refers to diabetes.										

Table 1: HbA1C, FBS and RBS concentrations in the diabetic and non-diabetic groups of the diabetic tests

Groups	Total No. of samples for each group	Mean ± SE of Toxo IgG UI/mL	Upper Value	Lower Value	Mean ± SE of Toxo IgM UI/mL	Upper Value	Lower Value
Diabetic patients with toxoplasmosis	51 (26.98%)	34.95 ± 7.5 a	217	0.6	0.082 ± 0.0052 a	0.2	0.02
Diabetic patients	58 (30.69%)	0.024 ±0.058 b	2.3	0.0	0.072 ± 0.003 a	0.16	0.02
Toxoplasmosis patients (control positive)	30 (15.87%)	32.7 ± 8.45 a	230	5.8	0.10 ± 0.04 b	0.19	0.01
Healthy individuals (control negative)	50 (26.46%)	0.38 ± 0.055 b	2.5	0.0	0.042 ± 0.005 ab	0.13	0.01
LSD value		0.218 *			0.0595 *		
P-value		0.0392			0.0478		
The differences between the various letters in the same column are statistically significant Significant * (P≤0.05), Highly significant ** (P≤0.01).							
Reference range of Toxo IgM: Primary (acute) infection ⩾ 0.6. **Reference range of Toxo IgG**: Secondary (chronic) infection ⩾ 3.0							

Table 2: Specific anti-Toxoplasma IgG and IgM in the case groups.

Groups	Total No. of samples for each group	Mean ± SE pg/ml	Upper Value	Lower Value
Diabetic patients with toxoplasmosis	30	102.3 ± 7.05 c	191.58	25.723
Diabetic patients	30	138.38 ± 5.69 b	185.3	100.38
Toxoplasmosis patients (control positive)	30	115.45 ± 4.44 bc	149.62	88.66
Healthy individuals (control negative)	30	320.43 ± 17.64 a	488.74	222.84
LSD value	32.382 **			
P-value	0.0001			
The differences between the various letters in the same column are statistically significant Highly significant ** (P≤0.01).				

Table 3: Comparison of IL-10 (pg/ml) in the sera of the diabetic patients and control groups.

highly significant differences in comparison with the other study groups.

Discussion

Diabetics are more susceptible to parasitic infections due to possible immune system suppression, neuropathy, and blood loss [23]. Several of the immunological disorders of diabetes have been highlighted in studies of patients with diabetes, including dysregulation of innate immunity, decreased T-cell responses, decreased neutrophil function, and humoral disorders [24]. Therefore, these patients may be susceptible to opportunistic infections such as *T. gondii* infection. Hence the timely detection of *T. gondii* in at risk people can avoid progressive disease and its consequences [25].

The results of table (1) matched with the results of Elkholy *et al.* [26] in HbA1C test that shown only 15/50 of toxoplasmosis patients had glycated hemoglobin. A glycated hemoglobin test can be used for early diagnosis to avoid inexpensive blood tests [27]. HbAlc test is considered an effective method for monitoring diabetes management [28]. Glycated hemoglobin is a routinely utilized marker for long-term glycemic control [29].

Immunocompromised hosts, especially those with weak cell-mediated immunity are at risk of developing widespread disease as a result of reactivation and exacerbation of chronic infections, such as those occasionally seen in diabetic patients [30].

However, in some comparisons there were clear differences when comparing a group of diabetic patients with toxoplasmosis with a control group. In general, interleukins including IL-10, play important roles in the response to injury and infection [31]. Interleukin 10 is an immunomodulatory cytokine that plays a central role in the progression of inflammation. A key role of IL-10 is to act as an essential inhibitory cytokine against the actions of pro-inflammatory cytokines such as IL-12 [32,33].

Interleukin type IL-10 has the ability to prevent the synthesis of pro-inflammatory cytokines such as IL-2, IL-3, IFN-γ, TNF-α and GM-CSF. However, it exhibits a potent capability to suppress the capacity of antigen presenting cells (APCs) and mast cells, thereby inducing maturation of B cells and producing antibodies that also stimulate specific T cells (Th2). Thus, IL-10 produced by mast cells that responds to inflammatory effects [34].

Interleukins and diabetes are closely related to their onset and progression. Variations in the concentration of specific interleukins in the body can indirectly affect the immunological vitality of diabetic patients, which not only aids in the diagnosis, prognosis and treatment of diabetes but also contributes to the development of diabetes. It is also useful for monitoring [35]. Increased T2DM is associated with the secretion of proinflammatory cytokines, and decreased IL-10 gene expression leads to increased production of these cytokines, which is detrimental [36]. The immune response was dominated by IL-10, which suppressed IL-6 and TNF-α production and promoted Th2 cell responses and antibody formation by B lymphocytes [37].

Th2 lymphocytes have specific cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, and IL-13) that can downregulate cell-mediated immune effector mechanisms that are particularly important for host defense against intracellular pathogens especially parasitic disease [38, 39]. Kanash and Yousif [40] studied IL-10 levels in women with breast cancer infected with toxoplasmosis and found that IL-10 levels raised in a group of women with breast cancer and toxoplasmosis, followed by those in women with breast cancer only in comparison with healthy control group which refers to the fact that the presence of *T. gondii* had a profound effect on cellular immune responses through increased IL-10 levels. This is due to the parasite's ability to increase the production of cytokines of Th2 cells including IL-10.

Author contributions

Sarah Ali Saeed: Conceptualization, writing-original draft, methodology, data curation.
Israa Kasim Al-Aubaidi: Supervision, writing-review and editing.

Competing Interests

The authors declared that there were no conflictsof interest.

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