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Article

Study of Some Immunological Aspects of Diabetic Type1 Infected with Toxoplasmosis

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Abstract: The present investigation was conducted on type 1 diabetes individuals infected with the *Toxoplasma* gondii parasite. The potential association between toxoplasmosis infection and type 1 diabetes (1DM) remains under investigation. This study aims to examine the role of interleukin-2 and interleukin-17 in the immune response to parasites. A total of 160 serum samples were obtained from Thi-Qar hospitals and private laboratories, categorised into four groups: 40 samples from type 1 diabetes patients infected with toxoplasmosis, 40 samples from type 1 diabetic patients only, 40 samples from patients with toxoplasmosis only, and 40 samples from the control group. The study results indicated that the serum concentration of IL-2 was highest in the type 1 diabetes group infected with toxoplasmosis, followed by the type 1 diabetic group alone, then the toxoplasmosis-infected group, with the control group exhibiting the lowest concentration. The IL-17 serum levels were elevated in the toxoplasmosis-infected group, followed by the type 1 diabetes group infected with toxoplasmosis, while the control group had the lowest concentration.

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1. Introduction

Toxoplasmosis is a prevalent disease caused by *Toxoplasma* gondii, an apicomplexan protozoan intercellular parasite that has infected over one-third of the global population (Al-Shamma, 2014). *Toxoplasma* infects all warm-blooded mammals, particularly those in the Felidae family (Tender et al., 2000). The disease occurs through the ingestion of oocysts via food or water, through tissue cysts in raw meat, and tachyzoites may infect embryos from pregnant moms infected with toxoplasmosis (Mahami et al., 2017; Master, 2015). In the majority of cases, acute toxoplasmosis infection is asymptomatic. Acquired infections are typically linked to reticular cell hyperplasia and lymphadenopathy (Torgerson and Mastroiacovo, 2013). Toxoplasmosis can induce severe illness in immunocompromised individuals, including those with HIV or those undergoing immunosuppressive therapy (Alavi and Alavi, 2016; Mohraz et al., 2011). *Toxoplasma* gondii infection stimulates the synthesis of various pro-inflammatory cytokines (TNF-α; IL-1; IL-15; IL-17), anti-inflammatory cytokines (TGF-β; IL-4; IL-10), reactive oxygen species, and nitric oxide synthase, which are linked to inflammatory responses in multiple tissues and cells, including the brain, astrocytes, microglial cells, and infiltrating CD4+ and CD8+ T cells. (Henriques et al., 2009; VanWormer et al., 2014). Research on human vaccines for the treatment of *Toxoplasma* gondii is underway; however, no effective human vaccine has been developed to yet (Zhang et al., 2022).Insulin-dependent diabetes mellitus (IDDM), or type I diabetes, is a devastating chronic condition that disrupts the synthesis and secretion

of the essential hormone insulin and modifies glucose metabolism. Insulin is produced and released by the pancreatic islet cells of Langerhans (WHO, 2014). The signs of diabetes include weight loss, polyuria, and thirst, along with other manifestations such as weariness, vaginal itching, blurred eyesight, and Candida infection (Feather et al., 2021). Type 1 diabetes mellitus occurs due to the death of insulin-producing beta cells in the pancreatic islets, resulting in insulin insufficiency. The primary cause of type 1 diabetes is an immune-driven process, specifically an autoimmune attack mediated by T cells, resulting in the destruction of beta cells and insulin deficiency. Type 1 accounts for 5 to 10% of diabetic cases and is the most frequently diagnosed type in children under 20 years of age. Type 1 diabetes can impact both children and adults, sometimes termed juvenile diabetes due to its frequent manifestation in youth. (Rother, 2007). Interleukin-2 (IL-2) is a cytokine regarded as a signalling molecule inside the immune system. It is a protein with a molecular weight of 15.5–16 kDa that modulates the activity of leukocytes, particularly lymphocytes, involved in the immunological response. IL-2 is a component of the human innate immune response to microbial infection, distinguishing between foreign "non-self" and "self" entities. Consequently, IL-2 exerts its effects by attaching to IL-2 receptors located on cells. The primary sources of IL-2 are activated CD4+ T cells and CD8+ T cells.Liao et al. (2011) IL-2 is essential to the immune system, influencing both tolerance and immunological response through its direct effect on T cells in the thymus gland. Following T cell maturation, it can prevent autoimmune disorders by facilitating the differentiation of immature T cells into regulatory T cells. IL-2 facilitates activation-induced cell death (AICD). Arenas-Ramirez et al. (2015). IL-2 facilitates the differentiation of T cells into effector and memory T cells following initial antigen-induced activation, hence augmenting the human body's capacity to combat infections.(Liao et al., 2011) Similar to other cytokines, IL-2 facilitates the differentiation of naive CD4+ T cells into Th1 and Th2 lymphocytes, while inhibiting the differentiation into Th17 and T helper lymphocytes.Liao et al. (2013). Interleukin (IL-17) is a pro-inflammatory cytokine produced by a distinct population of T-helper cells known as T-helper 17 cells, in response to IL-23 activation. Th17 was identified in 1993 by Rouvier et al., who recovered the IL-17 transcript from a rodent T-cell hybridoma. Starens et al. (2002) IL-17 attaching to its receptor initiates multiple signalling cascades that stimulate the synthesis of chemokines. These chemokines work as chemoattractants, drawing immune cells including neutrophils, lymphocytes, monocytes, and innate immune cells to the site of inflammation. All signalling events react to the intrusion of pathogens into the human body. Enhancing the inflammatory and antimicrobial functions (Chiricozzi et al., 2011; Hajishengallis, 2014; Miossec et al., 2009). Although IL-17 can promote the production of antimicrobial substances by epithelial cells, extensive research demonstrates that IL-17 signalling predominantly contributes to disease progression, as shown by studies in both human and animal models.Iwakura et al. (2011), Eskan et al. (2012), Miossec and Kolls (2012). This study aimed to determine the role of IL-2 and IL-17 in Type 1 diabetic patients relative to other groups and controls, to clarify the potential link between Toxoplasmosis and Type 1 diabetes using ELISA technology.

2. Materials and Methods

Study Groups

The Study groups divided into four (a group of Type1 diabetic patients infected with Toxoplasmosis , a group of Type1 diabetic only, a group of Toxoplasmosis patients only and control group).

Collection of samples

The study samples were collected from Thi-Qar hospitals and private laboratories for the periods started from 1st of September 2018 to the end of July 2019. A total of 60

samples of type1 diabetic were diagnosed infected with *Toxoplasma* gondii parasite from 350 samples ,while 260 samples were infected with type1 diabetes only , 30 samples collected from patients infected with Toxoplasmosis only and 30 samples as a control. We collected blood samples from each patients then separated serum by using gel tubes and centrifuge for (5-10)minutes on (2500-3000)c/min ,Then freeze samples under -20c° , we used 30 sample from each group to detection the concentration of IL-2 and IL-17 by ELISA technique

Using Enzyme-linkedImmuno Sorbent Assay (ELISA) to calculate concentration of Cytokines (IL-2 and IL-17)

Assay procedure

The primary steps of this approach involve adding 100 µL of standard or sample to each well. Incubate for 90 minutes at 37°C, remove the liquid, and add 100 µL of HRP Conjugate. Incubate for 30 minutes at 37°C. Aspirate and wash five times, then add 90 µL of substrate reagent. Incubate for 15 minutes at 37°C, add 50 µL of Stop Solution, and read at 450 nm immediately; finally, calculate the results.

3. Results

Interleukine- 2 result

The current study recorded highest concentration of IL-2 in type1 diabetic patients infected with Toxoplasmosis group which recorded (343.02 ± 59.30)pg/ml , then type1 diabetes mellitus only group which recorded (289.59 ± 52.92)pg/ml, then Toxoplasmosis infected group which recorded (197.86 ± 53.98)pg/ml , compared with control group which recorded the lowest concentration of IL-6 which recorded (87.12 ± 17.55)pg/ml.

Table 1. Interleukin -2 concentration in study groups.

Samples	IL-2
Diabetic 1+toxoplasmosis	343.02 ± 59.30
Diabetic type1	289.59 ± 52.92
Toxoplasmosis	197.86 ± 53.98
Control	87.12 ± 17.55
L.S.D	**35.67**
p-value	**0.0001**

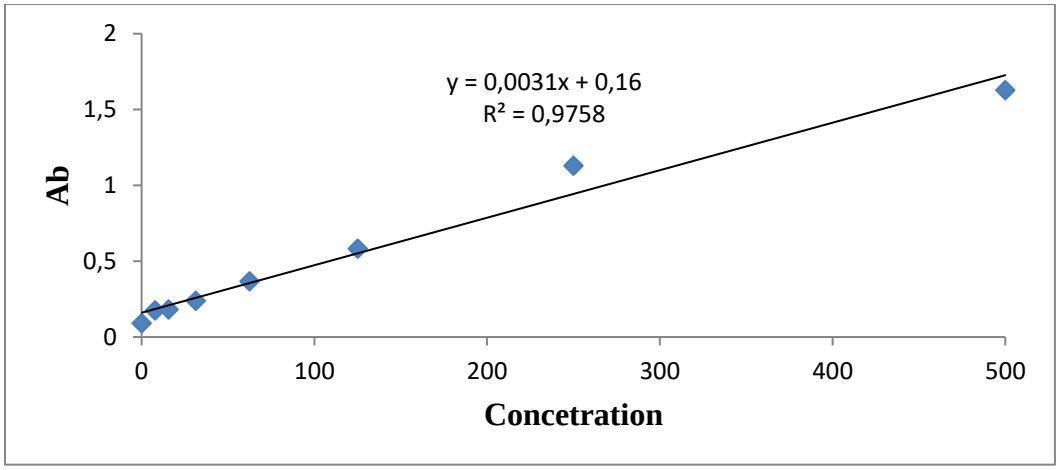

Figure 1. The Standard curve of Interleukine -2 concentration in study groups.

Interleukine -17 result

The study recorded highest concentration of IL-17 in Toxoplasmosis infected group which recorded (426.09 ± 21.59)pg/ml, then type1 diabetes mellitus infected with Toxoplasmosis group which recorded (405.21 ± 43.66a)pg/ml , then type1diabetes mellitus only group (367.48 ± 34.78b)pg/ml , compared with control group which recorded the lowest concentration of IL-12 (299.09 ± 18.35c)pg/ml .

Table 2. Interleukin -17 concentration in study groups.

Samples	IL-17
Diabetic 1+toxoplasmosis	405.21 ± 43.66a
Diabetic type1	367.48 ± 34.78b
Toxoplasmosis	426.09 ± 21.59a
Control	299.09 ± 18.35c
L.S.D	23.04
p-value	**0.0001**

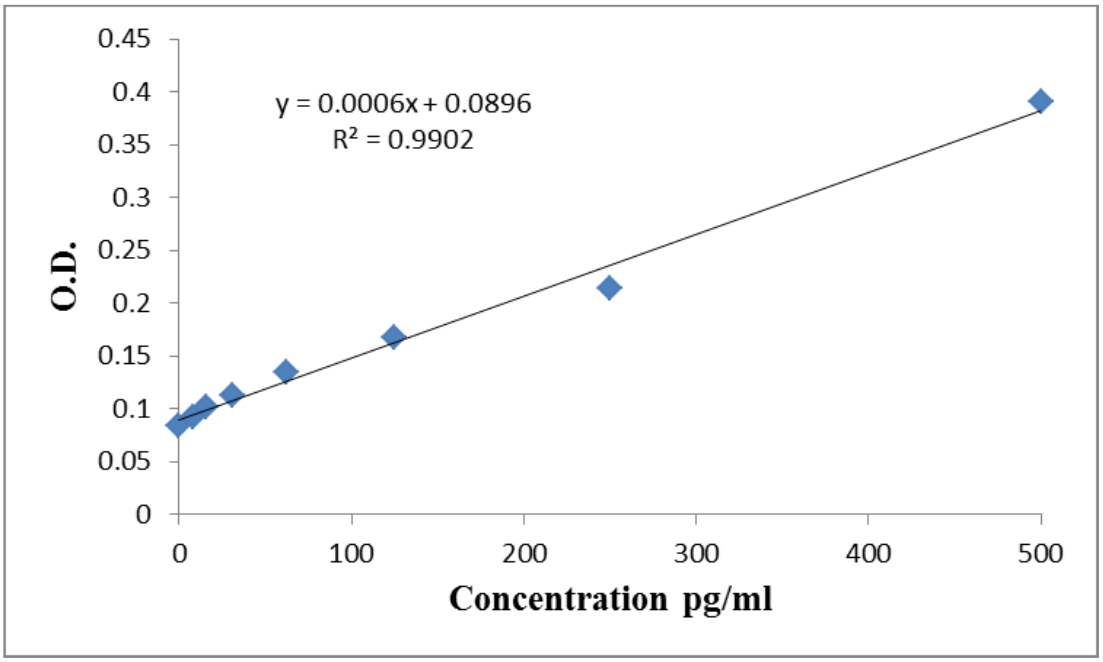

Figure 2. The Standard curve of Interleukin -17 concentration in the study groups.

4. Discussion

Toxoplasma infection is prevalent in immunocompromised people (Dubey, 2005). diabetes patients were categorised as immunocompromised individuals (Olefsky, 1985); hence, Toxoplasmosis in type 1 diabetes individuals may result in severe or chronic illness. Toxoplasmosis in most immunocompetent individuals manifests with nonspecific signs and is often asymptomatic. Most recover without treatment (Kankova, 2015) due to an effective immune system. However, in immunocompromised individuals, *Toxoplasma* can replicate in any nucleated cell, inducing various inflammatory markers through both innate acute inflammatory responses and antigen-specific adaptive immunity, ultimately resulting in chronic infection (Prandota, 2013). This study found significant increasing of interleukin -2 in the group of type 1 diabetes infected with Toxoplasmosis ,then the group of type1 diabetic only ,then the group of Toxoplasmosis only ,compared with control which recorded lowest concentration. IL-2 has acritical role in immune response against

Toxoplasma gondii because it enhance the activation of induced cell death (Arenas-Ramirez,2015), IL-2 also induce the differentiation of T cells into active (effector) T cells , memory T cells when its stimulate by antigen ,so IL-2 helping the body to fight any infection by invading organisms (Liao,2011) ,together with cytokine , IL-2 can stimulate naïve CD4+ T cells into Th1 and Th2 ,also involve in activation of Th17 lymphocytic response.(Liao,2013). The present study found significant increasing of interleukin -17 in the group of type 1 diabetes infected with Toxoplasmosis then the group of type1 diabetic only, then the group of Toxoplasmosis only, compared with control which recorded lowest concentration. The IL-17 has been linked with many immune and autoimmune diseases, also has acritical role in immune regulatory function.IL-17 is involving to inducing and mediating pro-inflammatory responses and induce the production of other cytokine like (TNF-α, TGF-β,IL-1β,IL-6 and GSF) which have an important role in immune response against Toxoplasmosis . IL-17, also can induce the production of many cells like macrophages and endothelial cells.IL-17 is essential to subset of CD4+ Tcells that called T helper 17 (Aggarwal and Gurney,2002)

5. Conclusion

The study reveals significant findings regarding the immunological response in type 1 diabetic patients infected with Toxoplasma gondii, showing elevated levels of IL-2 and IL-17 compared to both non-infected diabetic patients and healthy controls. The heightened IL-2 levels, especially in diabetic patients co-infected with T. gondii, suggest an amplified immune response potentially contributing to the management of chronic infections in immunocompromised individuals. Similarly, the increase in IL-17 highlights its pro-inflammatory role in mediating immune responses to parasitic infections. These findings imply that cytokine modulation could be a promising therapeutic target in managing toxoplasmosis among diabetic patients. Further research is warranted to investigate the mechanistic pathways of these cytokines in chronic infections and their potential in developing immunotherapies for high-risk diabetic individuals.

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