ORIGINAL ARTICLE

Detection of *toxoplasma gondii* among Autoimmune Thyroid Disease (AITD) and Estimation of its Association with Transforming Growth Factor-β (TGF-β)

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ABSTRACT

Background*: Toxoplasmosis is the most common parasitic infection in the world, caused by T. gondii that is associated with a number of problems such as thyroid diseases, the most prevalent endocrine disorders secondary to diabetes.* ***Objectives****: This study aims to investigate the relationship between latent toxoplasmosis and autoimmune thyroid diseases and estimation of its association with the transforming growth factor.* ***Methodology*** *The study included 100 patients with AITD and 70 normal control who entered Thi-Qar Specialized Diabetes, Endocrine Center in Nasiriyah city, Southern Iraq. The samples were collected during a period from August to November (2023) using ElectrochemiLuminescence and ELISA methods to determine the presence of AITD and anti T.gondii (IgG).* ***Results****: This study showed 33% of patients with AITD were infected with T. gondii and the age of them ranged between15-70 years, Additionally the current study showed an association between sex of patients with AITD infected T.gondii . Also, in the present study the level of TGF among Graves' patient infected with T.gondii was (170 ± 22.8 pg/ml) compared with Graves' patient without T.gondii, it was (171 ± 18.6) while in the control group it was (213.3 ± 31.6,177 ± 22.4) respectively, TGF.β level in patients with Hashimotos thyroiditis infected with T.gondii was (145.66 ± 18.6) compared with Hashimotos thyroiditis without T.gondii (133.11± 28.8) while the control group was (213.3 ± 31.6,177 ± 22.4) respectively.* ***Conclusion:*** *The molecular mimicry hypothesis suggests a resemblance between human thyroid autoantigens and molecular components of T.gondii; the generation specific autoantibodies against thyroid.*

INTRODUCTION

Toxoplasma gondii is an apicomplexan protozoan parasite that forms worldwide toxoplasmosis[1]. *T. gondii* infections in humans; especially in newborns and individuals with compromised immune systems are typically asymptomatic but can potentially result in a serious case of toxoplasmosis few weeks after exposure, it may induce minor flu-like symptoms but in healthy adult humans it rarely causes any symptoms[2]. *T.gondii* can take three infectious forms: tachyzoite (in the acute phase), bradyzoite (in the chronic phase) and sporozoites (which develop in the oocyst and are seen in the feces of cats)[3]. About one-third of all humans are infected with the protozoan parasite *T. gondii*, which can cause symptomatic and frequently fatal toxoplasmosis in immunocompromised people, such as those with AIDS or undergoing chemotherapy or immunosuppressive drug treatment, when *T. gondii* infects a pregnant woman, the fetus and the newborn are at risk of congenital disorders[4].

The transmission of *T. gondii* occurs with undercooked meat containing tissue cysts while oocysts shed consuming soil, water, vegetable and anything contaminated by the feces of an infected animal and another transfer by organ transplant, blood transfusion and transplacental transfer between mother and fetus[5].The parasite can infect all types of nucleated cells of the body. For this reason, it is presented in different tissues such as skeletal muscles, cardiac muscles and brain as well as thyroid that causes thyroiditis[6]. Thyroid gland inflammation is referred to as "thyroiditis". It can be brought by radiation, drugs, trauma, or outside factors like viruses and parasites[7].Hashimoto thyroiditis and Graves' disease are examples of autoimmune thyroiditis. In Hashimoto disease, antibodies against the thyroid gland can be formed as a result of a viral or parasitic infection that is similar in structure with the thyroid protein[8].while the Graves' disease (GD) in developed countries is the most common cause of hyperthyroidism.. It is an organ-specific autoimmune disorder linked to circulating TSH-R autoantibodies. Although it affects people of all ages, but most common effect is on females at the reproductive age[9]. *T.gondii*

may multiply and infect any nucleated host cell, which causes a number of inflammatory markers against antigen(*T.gondii*)[10] . The transforming growth factor (TGF-β) family of growth factors plays a major role in the development and homeostasis of the majority of human tissues and regulates a vast array of cellular responses[11]. Multifunctional for transforming growth factor-β (TGF-β) inhibits the proliferation, maturation, and/or activation of macrophages, lymphocytes, and natural killer (NK) cells, thus have an anti-inflammatory effects[12].

METHODOLOGY

Ethical clearance:

The current investigation was carried out in compliance with the Declaration of Helsinki's ethical guidelines. Before taking a sample, the patient's verbal and analytical consent was obtained. A local Ethics Committee examined and approved the study protocol, subject information, and permission during period extended from august to November (2023) in accordance with document number 159/2023.

Blood Samples

The current study included 100 patients with AITD they entered at Thi-Qar Specialized Diabetes, Endocrine & Metabolism Center (TDEMC) in Nasiriyah City, Southern Iraq. during the period which extended from August to November (2023) and 70 cases as healthy controls. Three ml of blood were collected from patients with AITD and left to clot, sera were isolated by centrifugation at 3000 rpm for 5 min and kept at -20°C until used[13].

Detection of anti-thyroid peroxidase anti bodies, TSH receptors anti bodies, *T.gondii* (IgG) antibody and Transforming growth factor ß(TGF-β)

Detection of anti TPO and TRAB was done by ElectrochemiLuminescence (cobas 411-Roshe-Germany) *and T.gondii* (IgG) antibodies were detected in patients with AITD and healthy controls by using toxoplasma IgG ELISA kit from Romania (cAMP, Romania). The ELISA technique was employed with a Sunlong kit from a Chinese company to determine the concentration of TGF.β in patients with AITD and controls with and without *T.gondii* according to the manufacturer's instructions.

Statistical Analysis:

The samples underwent statistical analysis according to Statistical Package for the Social Sciences (SPSS) Chi sequare ($\chi 2$) and p-value indicated level significant between the samples.

RESULTS

As shown in Table1, the current study revealed about 71(71%) of the total number of patients with Hashimoto thyroiditis who had thyroid peroxidase antibodies (anti TPO) were reported with a level 244 ±15.6 IU/ mL while 29 (29%) from patients with Graves' disease had TSH receptors antibodies with a level 14-0 ± 2.21 IU/mL.

Table 1: Level of TPO Ab and TRAB in Hashimoto's and Graves' patients

Cases	No. patients (%)	TPO IU/mL mean± SD	TRAB IU/mL mean± SD
Hashimoto thyroiditis	71(71%)	244 ±15.6	___
Graves' disease	29(29%)	___	14.0 ± 2.21
Total	100	___	___
Control		10.53 ±1.42	0.87± 0.06
p-value		0.000	0.001

X2 = 17.64 df = 2 (high significant difference P≤ 0.05**)**

The results of the present study showed 33% of patients with AITD infected with *T.gondii* (IgG). This revealed a significant difference through infection with *T.gondii* in patients with AITD, as shown in table 2.

Table 2: IgG level against *T.gondii* in patients with autoimmune thyroid disease

Patients	NO. AITD	%
AITD (TOXO +)	33	(33%)
AITD (TOXO -)	67	(67%)
Control (TOXO +)	22	(31%)
Control (TOXO -)	48	(69 %)

X2 = 26.0 df = 3 p-value= 0.01 significant difference P≤ 0.05

The age of patients with autoimmune thyroid disease ranged between (15–70) years old. The high rate (39.39%)of latent toxoplasmosis(IgG) were reported among AITD patients with age range between(35-44) while the low rate of infection was reported among patients with age range from (65-70) years old as shown in table 3**.**

Table 3: Age of patients with autoimmune thyroid disease with latent toxoplasmosis

Age	No. AITD (%) with latent toxoplasmosis
15-24	5 (15.15 %)
25-34	4 (12.12 %)
35-44	13 (39.39 %)
45-54	7 (21.2 %)
55-64	3 (9.09 %)
65-70	1 (3.03 %)
Total	33

X2 = 15.909 df = 5 p-value=0.002 (significant difference P≤ 0.05**)**

The current study showed a high rate(76%) of infections with latent toxoplasmosis(IgG) among AITD females while (24%) of males have latent toxoplasmosis (IgG) as listed in table 4.

Table 4: Sex of patients with autoimmune thyroid disease had latent toxoplasmosis

Sex	No %.AITD patient with latent toxoplasmosis
Male	8 (24 %)
Female	25 (76%)
Total	33

X2 = 16.50 df = 1 p-value=0.01 (significant difference P≤ 0.05**)**

Transforming growth factor (TGF.β) was tested during estimating the relationship between patients with Gravis disease and latent toxoplasmosis (IgG), The level of TGF. β in Gravis patients infected with *T.gondii* (IgG) was 170 ±22.8 pg/ml while the control group with *T.gondii* it was 213.3 ± 31.6 and without *T.gondii* was 177 ± 22.4 pg/ml, as shown in table 5.

Table 5: level of TGF.β among patients with Graves' disease with latent toxoplasmosis

Cases	Level of TGF(pg/ml) Mean ± SD
Graves' disease (TOXO +)	170 ± 22.8
Graves' disease (TOXO -)	171 ± 18.6
Control (TOXO +)	213.3 ± 31.6
Control (TOXO -)	177 ± 22.4

X2 = 6.83 df = 3 p-value=0.07 (Non-Significant differences P>0.05)

The level of TGF.β in patients with Hashimotos thyroiditis was (145.66 ± 18.6) and (133.11± 28.8) pg/ml with and without latent toxoplasmosis(IgG) respectively while in control groups were (213.3± 31.6) (177± 22.4) as listed in table 6.

Table 6: level of TGF among patients with Hashimoto's thyroiditis with latent toxoplasmosis

Cases	TGF.β Mean±SD
Hashimoto's disease (TOXO +)	145.66 ± 18.6
Hashimoto's disease (TOXO -)	133.11± 28.8
Control (TOXO +)	213.3± 31.6
Control (TOXO -)	177± 22.4

X2 = 19.29 df = 3 p-value=0.01 (significant difference P≤ 0.05)

DISCUSSION

Toxoplasmosis is a disease caused by infection with the protozoan parasite called *T. gondii* that is one of the most widespread parasite in the world. It is estimated that around one-third of the world's population is affected with the disease [14]. After infection, the parasite spreads to other body areas through lymph and blood. It has the potential to penetrate the pituitary and thyroid glands, influencing the generation of TSH and thyroid hormones [15].

The results of the current study indicated that Hashimotos thyroiditis is common, the reasons for such a high prevalence of AITD in the population remain unclear, with the multifactorial etiology being the most popular hypothesis. It is known that people with a genetic predisposition may develop AITD after an infectious disease [16] .The titer of antibody indicates the degree of lymphatic infiltration of the thyroid gland and is mostly produced by thyroid-infiltrating lymphocytes [17]. It would be possible to clarify the potential pathogenic involvement of serum anti-TPO antibodies in the production of hypothyroidism by comparing the levels of this antibody to the serum concentrations of thyroid hormones [18].

TRAB is another autoimmune marker for AITD and is important in the differential diagnosis of hyperthyroidism. This has significant consequences for prognosis and therapy. One important aspect of the GD pathophysiology is the autoimmune generation of TRAB [19] .

Thyroid hormones which are essential for regulating metabolism. as well as heart, brain, and bone functions, thyroid gland is one of the many organs and glands that *T. gondii* can attack[20]. When there is an imbalance in immunological tolerance, the body's immune system attacks the thyroid gland and its hormones, disrupting the hormone system. AITD causes the generation of specific autoantibodies that are directed against thyroid antigens due to molecular mimicry hypothesis which suggests the resemblance between human thyroid autoantigens and molecular components of *T.gondii* responsible for AITD characterized by hyper- or hypothyroidism[21].

The results of our study showed 33% of AITD were infected with *T.gondii* (IgG). this agreed with Mohammad study[22] that showed the Prevalence of

T.gondii (IgG) among patients with thyroid dysfunction was 31.9%.

Toxoplasmosis is the second most common foodborne infection. It is estimated that around one-third of the world's population is affected by the disease [23]. Within the Arabic- countries as well as the Middle East, toxoplasmosis rates vary by region. The Arabian Peninsula has been shown that toxoplasmosis seropositivity ranges from 22.9% to 58.2%. Pregnant Saudi women's overall toxoplasmosis seropositivity rate was 29.6%[20]. Recent clinical research have connected anti-*T.gondii* antibodies to certain autoimmune diseases. A range of diseases, including RA, SLE and AITD can be made more likely by infection with *T. gondii* [24]. *T.gondii* were determined in many studies involved diabetes, cancer, and COVID-19 that recorded (35%, 85.7% and 51.7%) respectively [25-27].

The current study showed the maximum seropositivity rate for *T.gondii* (IgG) antibody were observed among the 35-44 years old (39.39%), compared with the minimum *T.gondii* (IgG) positivity were among the 65-70 years old group (3.03%).

This differences in the prevalence of *T.gondii* according to the age may be due to the touch with oocysts, extended exposure to risk factors and transmission pathways, and a lack of toxoplasmosis prevention and control measures could all be contributing factors to this variation [28].

The results of the present study showed a significant difference in prevalence of toxoplasmosis between autoimmune thyroid patients based on their sex, where AITD females were more infected with *T. gondii* (76%) than males (24 %).

This may be due to the fact that elderly women work very hard around the house, especially when it comes to handling meats, making salads, cooking, and cleaning, and are therefore more likely to be exposed to the risk factors of toxoplasmosis and other diseases [29].

There are many different cell types that release a wide family of multifunctional proteins called TGF.β which function as signal molecules to regulate a wide variety of biological activities [30].

In our work, the level of TGF. B was (170 ±22.8 pg/ml) in Gravis patients who were suffering from latent toxoplasmosis(IgG) while Gravis patients who were not infected with *T.gondii* explain the level was (171 ± 18.6 pg/ml) in compared with control group (213.3 ± 31.6) and(177 ± 22.4) pg/ml respectively.

Our findings agreed with a study done by Maria P. *et al* [31] that explained reduced serum TGF-β levels enhance Graves' disease expression, heighten the risk of Hashimoto's thyroiditis and initiate the autoimmune process in its early stages, and stimulate autoimmunity in autoimmune thyroid disease .

TGF has a significant anti-inflammatory and immunosuppressive effects, with the latter effect being mediated by regulation of all effector immune cell activation, proliferation, differentiation, and survival [32].

The function of TGF-β during parasitic infection was explained by the essential roles that it plays in the development of Th17 and T regulatory cells, mucosal immunity, and control immune response of all them [33]. It has been shown that TGF. β regulates tissue homeostasis, development and remodeling, and disease states by acting both stimulatorily and inhibitorily [34].

The current study showed the level of TGF.β in Hashimotos thyroiditis patients with and without latent toxoplasmosis(IgG) was (145.66 ± 18.6) and (133.11± 28.8) pg/ml respectively.

TGF-β is essential for both the thyroid gland's physiology and the immune system's integrity. Moreover, there is a strong evidence linking this molecule to the onset and progression of thyroid autoimmunity. Numerous studies show that TGF-β has a significant role in thyroid autoimmunity diagnosis and prognosis [35].

The decreasing level of serum TGF-β concentrations have increase the susceptibility to Hashimoto's thyroiditis. trigger the immune phenomena defining the initial pathophysiologic stage of this disease, and are associated with increased risk for post-partum thyroiditis. Prolonged hyperthyroid phase, and increased autoantibody production in this disease [36]. In the early stage of the autoimmune process, TGF- β plays an inhibitory role, whereas it may trigger the development of fibrosis during the late stage of the disease as was shown in an experimental granulomatous thyroiditis model [37].

These cytokine slightly increased in control groups with latent toxoplasmosis due to production of anti-inflammatory TGF.β is a key to promoting regulatory T cells which help maintain immune tolerance and prevent immune mediated damage while keeping parasite in check and the production of TGF.β helping parasite to survive in a latent state within host tissue [34].

CONCLUSION

Our findings in this work indicates that AITD can be a target by *T.gondii* through immune inflammatory responses, which led to the thought of molecular similarities between thyroid autoantigens and *T. gondii* pathogen components and decreased TGF.β are suitable to develop Hashimotos thyroiditis.

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Author contributions

Akram and Amal conceptualized the project, conducted the experimental procedures, drafted the

initial articles, and conducted the statistical analysis. Akram and Amal managed the data collection. All authors collaborated on writing, reviewing, and editing the material. The authors have reviewed and approved the final manuscript.

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