

Association between T3, T4, and TSH hormones proportion and *Toxoplasma gondii* anti-IgG seroprevalence in patients suffering from clinical and drug-controlled thyroid dysfunctions in southeastern Iran

Güneydoğu İran'da klinik ve ilaç kontrollü tiroid fonksiyon bozukluğu olan hastalarda T3, T4 ve TSH hormonları oranı ile *Toxoplasma gondii* anti-IgG seroprevalansı arasındaki ilişki

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ABSTRACT

Objective: *Toxoplasma gondii* is an important agent responsible for many hormonal and behavioral disorders in humans. The main objective of this study was to evaluate the hypothesis that '*T. gondii* infection interferes with thyroid hormones secretion or thyroid drug treatment'.

Methods: This is a cross-sectional study that involved 249 patients suffering from thyroid dysfunctions, divided into 3 groups: hypothyroidism (n=107), hyperthyroidism (n=96), and drug-controlled thyroid disorders (n=91), referred to Seyedoshohada Kerman private clinic. Serum samples were tested for thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) along with *Toxoplasma* anti-IgG using ELISA technique. Demographic information was collected using a demographic sheet.

ÖZET

Amaç: *Toxoplasma gondii*, insanlarda birçok hormonal ve davranışsal bozukluktan sorumlu olan önemli bir ajandır. Bu çalışmanın temel amacı, '*T. gondii* enfeksiyonunun tiroid hormonlarının salgılanmasına veya tiroid ilaç tedavisine müdahale ettiği hipotezini değerlendirmektir.

Yöntem: Bu, Seyedoshohada'daki Kerman özel kliniği'ne yönlendirilen, tiroid disfonksiyonlarından muzdarip 249 hastayı 3 gruba ayıran kesitsel bir çalışmadır: hipotiroidizm (n=107), hipertiroidizm (n=96) ve ilaç kontrollü tiroid bozuklukları (n=91). Serum örnekleri tiroid stimulan hormon (TSH), triiyodotironin (T3) ve tiroksin (T4) ile *Toksoplazma* anti-IgG için ELISA tekniği kullanılarak test edildi. Demografik bilgiler bir demografik anket kullanılarak toplandı.

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Results: The seroprevalence of *Toxoplasma gondii* IgG antibodies among patients with hypothyroidism, hyperthyroidism, and drug-controlled thyroid disorders was 22.4%, 19.8%, and 22% respectively. The mean value of thyroid hormones of positive *T. gondii* samples in hypothyroidism, hyperthyroidism, and drug-controlled thyroid disorders was TSH=7.95, T3=1.12, T4=2.36; TSH=0.14, T3=1.42, T4=7.85; and TSH=2.75, T3=1.12, T4=1.45 respectively. The seropositivity of *Toxoplasma gondii* infection was 40.4% among individuals with a history of contact with pets and 26.3% among the rural dwellers.

Conclusion: There was no significant difference between *T. gondii* infection among the three study groups. A comparison of serum levels of thyroid hormones between infected and non-infected individuals in the above-mentioned groups illustrated that latent toxoplasmosis wasn't significantly associated with thyroid hormones secretion. Also, contact with pets and the rural lifestyle has a positive association with *T. gondii* seroprevalence.

Key Words: *Toxoplasma gondii*, hypothyroidism, hyperthyroidism, cross-sectional study, TSH, T3, T4

Bulgular: Hipotiroidizm, hipertiroidizm ve ilaç kontrollü tiroid bozukluğu olan hastalarda *Toxoplasma gondii* IgG antikörlerinin seroprevalansı sırasıyla %22.4, %19.8 ve %22 idi. Hipotiroidizm, hipertiroidizm ve ilaç kontrollü tiroid bozukluklarında pozitif *T. gondii* örneklerinin tiroid hormonlarının ortalama değeri TSH ;7.95, T3;1.12, T4;2.36; TSH;0.14, T3;1.42, T4;7.85; ve sırasıyla TSH;2.75, T3;1.12, T4;1.45 idi. *Toxoplasma gondii* enfeksiyonunun seropozitifliği, evcil hayvanlarla temas öyküsü olan bireylerde %40.4 ve kırsalda yaşayanlarda %26.3 idi.

Sonuç: Üç çalışma grubu arasında *T. gondii* enfeksiyonu arasında anlamlı bir fark yoktu. Yukarıda belirtilen gruplarda enfekte olan ve olmayan bireyler arasında serum tiroid hormon seviyelerinin karşılaştırılması, latent toksoplazmozun tiroid hormonlarının salgılanmasıyla önemli ölçüde ilişkili olmadığını gösterdi. Ayrıca, evcil hayvanlarla temas ve kırsal yaşam tarzı, *T. gondii* seroprevalansı ile pozitif bir ilişkiye sahipti.

Anahtar Kelimeler: *Toxoplasma gondii*, hipotiroidizm, hipertiroidizm, kesitsel çalışma, TSH, T3, T4

INTRODUCTION

Toxoplasma gondii is an obligatory intracellular parasite of worldwide distribution (1). It is an Apicomplexan protozoan that causes toxoplasmosis - an important zoonotic disease associated with high morbidity and mortality (2, 3). The disease is contracted essentially via the ingestion of tissue cysts in meat products or the intake of sporulated oocytes shed by cats into the environment (4). Clinical diagnosis of toxoplasmosis can be difficult since its clinical features are very similar to that of various illnesses (5). Latent toxoplasmosis is caused by the presence of tissue cysts in eyes leading to retina scars and eventual blindness (6) Infection with *T. gondii* affects about one-third of the world

population. Hence its prevention, diagnosis, and management should be an essential health priority (7). In addition, complications caused by *T. gondii* have an impact on maternal abortion (8). *Toxoplasma gondii* is practically accepted to cause miscarriages, intrauterine deaths or congenital abnormalities only as a result of the primary acute infection of the mother. Recurrent conditions such as infection with a different genotype or the tissue cyst in the uterine wall are all rare and accepted as negligible. As a result, *T. gondii* is not considered as a cause of recurrent abortion. Generally, all organ systems could be involved with disseminated toxoplasmosis with or without specific symptoms (9-19). Recently,

T. gondii is recognized as a target research in autoimmune thyroid diseases (20) and as a pathogen that accounts for other autoimmune diseases (8, 21, 22). Some studies illustrated that *T. gondii* is responsible for thyroid hormones alterations, consequent to changes in thyroid morphology and function; initial infection with *T. gondii* dramatically increases thyroid peroxidase (23, 24). Another study advocates that chronic toxoplasmosis can alter the stimulation of the hypothalamus, thus, alters T3, T4 secretion and results in TSH disturbance (13, 23). Based on the previous literature we hypothesized that chronic *T. gondii* infection can upset the serum level of thyroid hormones. Hence, the present study aimed to evaluate the serum thyroid hormones levels among members of the three study groups with thyroid dysfunctions and then compared data to that of the control (non-infected cases) in each group. Besides, the study evaluated the role of *T. gondii* in treatment of thyroid dysfunction disturbance. To our knowledge, this is the first time that the effects of *T. gondii* infection on drug treatment has been investigated among patients suffering from thyroid disorders.

MATERIAL and METHOD

This study was approved by the Zahedan University of Medical Sciences Ethics Committee (Date: 24.01.2020 and Number: IR.ZAUMS.REC.1399.486).

Study Design

This is a cross-sectional study involving 249 patients suffering from thyroid disorders - hypothyroidism (n=107), hyperthyroidism (n=96) and drug-controlled thyroid disorders (n=91) - referred to Seyedo Alshohada private clinic in Kerman city, southeastern IRAN. The study was performed between February 2018 and July 2019. All the participants gave their consent before the commencement of the study. We recorded the patients' demographic information, history about their locations, contact with pets,

meat product consumption, and pica behavior by demographic sheet. We collected 5 mL of blood from each patient, centrifuged the blood at 3000 rpm for 10 minutes, and then stored in 4 separate Eppendorf tubes at -20°C, till the next test.

Serological and Hormones Evaluations

Anti-IgG for *T. gondii* was measured using the *Toxoplasma* IgG ELISA kit (PISHTAZ TEB, Iran). We compared the OD of each sample with the cut-off value and recorded. We analyzed the hormones by TSH ELISA Kit (AUTOBIO- Zhengzhou, China), T3 ELISA kit (IDEAL-Tehran, Iran), and T4 ELISA Kit (AUTOBIO- Zhengzhou, China) according to the manufacturer's guidelines. Normal ranges of hormones kits were: TSH normal range: 0.3 - 5.5 µl U/ml, T4 normal range: 4.5 - 13 µg/dl, and T3 normal range: 0.55 - 1.9 ng/ml.

Statistics analysis

In this study, we used SPSS software version 20 for statistical analyses of our data. We compared the thyroid hormones and seroprevalence of *Toxoplasma* anti-IgG in the three groups (hypothyroidism, hyperthyroidism, and drug-controlled thyroid disorders) using independent sample T-test. Evaluation of independent variable efficacy (positive *T. gondii* anti IgG) over the dependent variables (thyroid hormones) along with the effect of demographic factors on IgG seroprevalence were assessed by multiple invariant analysis of variance (ANOVA) and Chi-Square test respectively. P-value ≤ 0.05 was considered significant in all the tests.

RESULTS

A total of 294 patients - referred to Seyedo Alshohada private clinic in Kerman, southeastern Iran - were recruited in this study and were divided among three groups: hypothyroidism (n=107), hyperthyroidism (n=96) and drug-controlled thyroid disorders (n=91). The study population consists of 135(54%) men and 114(46%) women. Their mean

age was 49.4, 56.7, 41.3 years for hypothyroidism, hyperthyroidism, and drug-controlled thyroid disorders groups, respectively. Our study findings showed that *T. gondii* infection doesn't have a

significant correlation with thyroids dysfunction. The seroprevalence of toxoplasmosis among patients with thyroid disorders was summarized in Table 1.

Table 1. Percentage distribution of Thyroid disorders patients infected with *Toxoplasma* by ELISA

Group	ELISA test						P-value
	Positive IgG		Negative IgG		Total		
	N	%	N	%	N	%	
Hypothyroidism	24	(22.4 %)	83	(77.6%)	107	(36.4%)	P>0.05
Hyperthyroidism	19	(19.8%)	77	(80.2%)	96	(32.6%)	
Drug-controlled thyroid disorder	20	(22,0%)	71	(78,0%)	91	(31,0%)	
Total	63	(21.4%)	231	(78.6%)	294	(100,0%)	

We compared the level of TSH, T3, T4 hormones among patients with hypothyroidism, hyperthyroidism and drug-treated thyroid dysfunction and found that there aren't significant statistical differences in hormones concentration between infected and non-

infected individuals. The mean concentration of the thyroid hormones (TSH, T4, and T3) in sera of thyroid disorders patients with toxoplasmosis (IgG-positive), by age groups and gender, are shown in Table 2 and 3.

Table 2. Association between the mean concentration of hormones (TSH, T4, and T3) in sera thyroid disorders patients with toxoplasmosis (IgG-positive) by age group, Iran

Age group	Mean concentration of Thyroid hormones in Thyroid disorders									P-value
	Hypothyroidism mean ± SD			Hyperthyroidism mean ± SD			Drug-controlled thyroid disorder mean ± SD			
	TSH	T4	T3	TSH	T4	T3	TSH	T4	T3	
20-40	7.00 ±0.5	1.50±0.5	1.00±0.5	0.08±0.02	7.80±2.1	1.40±0.51	4.25±0.35	7.00±1.41	1.25±0.35	P>0.05
41-60	8.03±1.64	2.53±0.71	1.03±0.3	0.10±0.04	9.18±1.9	1.15±0.46	1.59±0.7	7.54±2.16	1.29±1.23	
61≤	8.64±1.37	2.35±1.21	1.14±0.47	0.14±0.06	7.33±0.68	1.04±0.29	1.85±1.13	6.35±1.93	0.96±0.3	

Table 3. Association between the mean concentration of hormones (TSH, T4, and T3) in sera thyroid disorders patients with toxoplasmosis (IgG-positive) by gender, Iran

Gender	Mean concentration of Thyroid hormones in Thyroid disorders									P-value
	Hypothyroidism mean ± SD			Hyperthyroidism mean ± SD			Drug-controlled thyroid disorder mean ± SD			
	TSH	T4	T3	TSH	T4	T3	TSH	T4	T3	
male	7.73±1.26	2.26±0.79	1.19±0.34	0.11±0.05	8.18±2.21	1.06±0.39	1.80±1.32	7.88±2.23	0.86±0.22	P>0.05
female	8.66±1.78	2.50±1.08	1.19±0.39	0.10±0.05	8.27±1.55	1.27±0.45	2.06±1.02	6.40±1.62	1.43±1.20	

We evaluated the demographic and behavioral factors of each participant. We found, among the *Toxoplasma* seropositive, that 7 (20.6%) had a positive history of pica, 46 (40.4%) had direct contact with cats, 5 (35.7%) had a history of frequent raw meat consumption, and 41 (26.3%) lived in the rural areas. However, neither history of pica nor raw meat

consumption had a statistically significant association with seropositivity to *T. gondii*, while direct contact with cats and living in rural areas had a statistically significant association with seropositivity to *T. gondii* (P -value ≤ 0.05). The distribution and association between these factors and toxoplasma seropositivity among the study population are shown in Table 4.

Table 4. Investigation of Factors Affecting *Toxoplasma* seropositivity among the study populations, Iran

Variables	Samples		Positivity		P-value
	N	(%)	N	(%)	
Pica					
Yes	34	(11.6%)	7	(20.6%)	$P > 0.05$
No	260	(88.4%)	52	(20.0%)	
Contact with cats					
Yes	114	(38.8%)	46	(40.4%)	$P \leq 0.05$
No	180	(61.2%)	17	(9.4%)	
Consumption of raw meat					
Yes	14	(4.8%)	5	(35.7%)	$P > 0.05$
No	280	(95.2%)	58	(20.7%)	
Location					
Rural area	156	(53.1%)	41	(26.3%)	$P \leq 0.05$
Urban area	138	(46.9%)	22	(16.0%)	

DISCUSSION and CONCLUSION

T. gondii infection affects the multi-organ functions via hormones alteration. Some studies showed a defined correlation between *T. gondii* infection and a change in testosterone, cortisol, dopamine, and other hormones secretion (25, 26). The objective of our study was to assess the effect of latent toxoplasmosis on thyroid hormones in hypothyroidism and hyperthyroidism. Furthermore, we evaluated whether toxoplasmosis could interfere with the drug treatment of thyroid dysfunction. Our study findings showed that *T. gondii* infection doesn't significantly affect the serum concentration of thyroid hormones among patients with thyroid dysfunction. The rates of *T. gondii* infection positivity in all study

groups were approximately similar. According to our data, the seroprevalence of toxoplasmosis was higher among patients that live in rural areas. Some researchers have proven the association between toxoplasmosis and rural lifestyle with probable link to frequent contact with cats (27, 28). In our study, we analyzed hormone concentrations in three groups by their age and gender subgroups, there wasn't a significant difference in hormone concentrations in different subgroups. Some studies claim that *T. gondii* has a protective role in hypothyroidism in patients less than 50 years old and suggested that it can be used to treat hypothyroidism (15). In contrast to the previous study, a survey of dogs suffering from thyroid dysfunctions reported two positive cases of toxoplasmosis that developed hypothyroidism six

months after treatment (23). In this study, latent *T. gondii* didn't show any correlation with thyroid dysfunction in general and results reject the hypothesis that *T. gondii* can be used to treat or ameliorate hypothyroidism. Kenova Sarka et al. corroborated our finding that latent toxoplasmosis has no association with thyroid hormones alteration. Moreover, they observed a mild decrease in TSH and an increase in T4 secretion in pregnant women infected with *T. gondii* (29). This little alteration of hormones might be related to HCG hormones in pregnant women, which has a TSH-like effect causing temporary gestational hyperthyroidism in pregnancy (30). A significant decline in T4 and an increase in T3 and TSH hormones were reported in pregnant women who had miscarriage from chronic toxoplasmosis (31). Also, another research confirmed that non-pregnant women with toxoplasmosis have significantly lower serum levels of TSH in comparison to non-infected control group, whereas, there weren't difference in T3 and T4 (32). Salman and Mustafa (2014), claimed that *T. gondii* infection could decrease levels of thyroid hormones (33). Mice infected with *T. gondii*

Curnell strains showed a decline in serum thyroxine (T4) levels (34). Furthermore, an impaired thyroid function was recorded in murine infected by *T. gondii*. A decline in serum thyroxine (T4) occurs in NYLAR female mice infected with *T. gondii* (35). Controversial results of our and other's study findings show that the association of toxoplasmosis with thyroid dysfunction remains in darkness. Although in our survey we didn't find any relation between chronic toxoplasmosis and thyroid hormones alteration, further research will needed to evaluate the actual mechanism of interaction between *T. gondii* infection and thyroid dysfunction.

In conclusion, our study illustrated that the presence of toxoplasmosis infection doesn't significantly alter thyroid hormones secretion in patients with thyroid disease. Due to the approximately similar mean proportion of TSH, T3 and T4 hormones in hypothyroidism and hyperthyroidism and the control groups. We can conclude that the infection with *T. gondii* had no specific role in the disturbance of serum levels of thyroid hormones.

ETHICS COMMITTEE APPROVAL

* The study was approved by the Zahedan University of Medical Sciences Ethics Committee (Date: : 24.01.2020 and Number: IR.ZAUMS.REC.1399.486).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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