RESEARCH ARTICLE

The Probable Association between Type 2 Diabetes Mellitus and *Toxoplasma gondii* Infection

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic disorder that constitutes a major health problem worldwide. *Toxoplasma gondii* is an intracellular parasite that may infect any nucleated cell. Toxoplasmosis is becoming a worldwide health threat, infecting 30–50% of the world's human population. The studies that have been undertaken to investigate the link between *T. gondii* infection and diabetes have shown contradictory findings. This research aimed to look at the possible link between T2DM and *T. gondii* infection.

Methods and Subjects: The enzyme-linked immunosorbent assay (ELISA) approach was used to screen for *T. gondii* IgM and IgG antibodies in 69 patients with T2DM and 92 seemingly healthy persons as controls.

Results: The results demonstrate that all participants were IgM negative, the percentage of *T. gondii* latent infection was (52.1%) among patients with T2DM and (31.5%) among non-diabetic individuals. The frequency of infection differs significantly between diabetic and non-diabetic people. *T. gondii* infection was not linked to the studied risk factors.

Conclusion: There is serological evidence of a link between T2D and *T. gondii* infection. Furthermore, Toxoplasmosis is a risk factor for type 2 diabetes.

Keywords: Immunocompromised, Risk factor, Toxoplasmosis, Type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is one of the 21st century's most serious public health issues.[1] It is a chronic condition characterized by persistent hyperglycemia and changes in fat, sugar, and protein metabolism induced by defects in insulin synthesis, insulin activity, or both.[2] T2DM is a widespread metabolic condition,[3] with an estimated worldwide incidence of 8.5% among persons aged 18 and above.[4] There are several risk factors for T2DM, including genetic susceptibility, physical inactivity, and obesity.[5] Furthermore, there may be unrecognized risk factors contributing to the increased incidence of T2DM, such as low-grade inflammation produced by pathogenic infections.[6]

Toxoplasma gondii is a protozoan parasite that infects almost all warm-blooded animals, including humans. *T. gondii* is a global parasite that infects around 30% of the world's population.[7] Infection rates vary by area, ranging from 15 to 85% depending on environmental conditions, food patterns, and self-hygiene. Toxoplasmosis may induce a number of ambiguous symptoms, the majority of which are comparable to flu-like symptoms.[8,9] The infection is considered to be asymptomatic in immunocompetent individuals, and the patient heals without medication due to an effective immune system that inhibits the spread of vegetative tachyzoites.[10] Unless a person is immunocompromised or pregnant, they are not usually tested for *T. gondii* illness.[8,11,12] It is, nevertheless, lethal in immunocompromised people.[6,13] In all instances, the parasite stays detectable in the host's serum throughout the host's lifespan, producing latent or chronic toxoplasmosis.[10,14] Chronic toxoplasmosis has been associated to a number of immunological illnesses such as neurological problems, rheumatoid arthritis, and thyroid disease.[15] *T. gondii* may infect and multiply in any nucleated cell, including pancreatic cells, and may play a role in diabetes. DM, on the other hand, affects the innate and adaptive immune response, predisposing the patient to a variety of opportunistic parasites, including *T. gondii*.[1,16]

Previous research on the link between *T. gondii* and T2DM produced mixed findings. In this context, the present research

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sought to determine the seroprevalence of anti *T. gondii* IgG and IgM antibodies in the blood of T2DM Iraqi patients, as well as a control group of non-diabetic persons.

MATERIALS AND METHODS

The blood samples in the current study were collected from 161 Iraqi men and women. The excluded cases were patients receiving toxoplasmosis treatment, patients providing incomplete information during completion of the questionnaire, and patients with psychiatric disorders.

Subjects 69 were diagnosed with T2DM, aged between 37 to 65 years. These patients' samples were collected at the Specialized Center for Endocrinology and Diabetes, Baghdad, after being diagnosed by a specialist physician. All patients were diagnosed of establishing T2DM on the basis of medical history and laboratory tests according to the criteria of the American Diabetes Association.[17] The blood samples of 92 healthy controls group were obtained from apparently healthy subjects, aged from 35–65 years. The period of collecting samples were from February 2021 to August 2021. A total of 3 mL of blood was collected in a gel tube, free of anticoagulant to separate the blood and obtaining the serum by centrifugation for 10 minutes at 3000 rpm, to be examine for the presence of anti-toxoplasma antibodies by ELISA special kits (ACON, USA). Sera had been stored at −20°C until analysis. The procedure for quantifying specific anti-*T. gondii* IgG and IgM antibodies in serum were carried out per the manufacturer's instructions.

All participants in the current study gave their informed consent before sample collection. The study has been revied and approved by the college of pharmacy, University of Baghdad, Research Ethics Committee application no. 3102020C.

Statistical Analysis

Statistical analysis system-version 9.1 (SAS) was used to perform data statistical analysis to detect the effect of different factors in study parameters. To compare means, the least significant difference–LSD test (analysis of variation-ANOVA) was used. Post-hoc tests are used to investigate differences in the means of multiple groups. The chi-square test was used to make a significant comparison between percentages (0.05 and 0.01 probability).

RESULTS AND DISCUSSION

According to ELISA test, all samples were assessed for seropositivity of IgM and IgG *T. gondii*. IgM antibodies were negative in all samples, while anti-*T. gondii* IgG was detected, and according to the seroprevalence of latent infection (IgG antibodies), the participants were sub-divided into four groups (Tables 1 and 2):

- Group 1: 36 patients having T2DM and have *T. gondii* infection.
- Group 2: 33 patients having T2DM and not have *T. gondii* infection.
- Group 3: 29 patients having *T. gondii* infection and not have DM.
- Group 4: 63 apparently healthy individuals not known to have DM nor *T. gondii* infection (referred to as the control group).

Chronic low-grade inflammation contributes to the pathology and complications of T2D.[18] Numerous researches have been undertaken to evaluate the link between T2DM and toxoplasma infection. The results of current study revealed that IgM antibodies were negative in all samples, while anti- *T. gondii* IgG was detected, *T. gondii* latent infection was 52.1% of T2DM patients and 31.5% of non-diabetic persons (Tables 1 and 2). This finding was consistent with a number of studies. Saheb EJ, 2017 conducted one of these studies in Iraq to investigate the seroprevalence of *T. gondii* infection in T2DM patients, in which 172 diabetic patients and 98 healthy individuals were tested for anti-*T. gondii* IgG antibodies using an ELISA test, and it was discovered that 55.8% of T2DM patients were IgG seropositive, compared to 38.8% of healthy individuals ($p < 0:01$).[19] Another study in Iraq by Molan *et al*., observed similar percentages (T2DM, 300/450, 66.6%; control, 68/203, 33.4%; $p = 0:009$).[20] In Iran, two studies by Saki *et al*., and Shirabazou *et al*., found that diabetes, 47/110, 42.7%; control, 24/110, 21.8% (p 0:05) and diabetic, 55/91, 60.4%; control, 36/93, 38.0% (p 0:001), respectively.[21,22] Furthermore, in Egypt Hemida *et al*., observed that T2DM, 14/37, 37.8%; control, 12/50, 24% ($p < 0:04$) and a study in Turkiye by Gokce *et al*., found that T2DM (457/807, 56.6%; control, 56/250, 22.4%; $p < 0:001$).[23,24]

On the other hand, some researches have shown no relationship between T2DM and *T. gondii* infection. Anti-*T. gondii* IgG antibodies were found in 52.6% of diabetes patients and 50.6% of healthy people in Iranian descriptive case-control research in which 150 diabetic patients and 150 healthy people were tested using an ELISA technique for anti-*T. gondii* IgG antibodies.[25] Furthermore, no serological evidence of a link between *T. gondii* infection and diabetes mellitus was found in an age and gender matched case-control study done in Mexico.[26] Furthermore, a recent age and gender matched case control study in Australia revealed no relationship between T2DM and *T. gondii* infection susceptibility, with IgG antibody seropositivity being 62% for T2DM patients and 66% for healthy controls. This argument might be ascribed to genetic causes and racial susceptibility differences favoring the Middle East.[27] Single nucleotide polymorphism in proinflammatory mediators (such interleukin 1, TNF, and IFN-γ) and anti-inflammatory cytokines (like Interleukin 10) might be a factor in this variance.[28, 29] "The cytokine system's genetics have a significant impact on a person's chance of contracting or developing an infectious or autoimmune illness".[30]

Additional systematic reviews and meta-analyses undertaken to examine the probable link between diabetes mellitus and toxoplasmosis indicated that *T. gondii* is a possible diabetes risk factor, and that additional study is required.[31-33]

The effects of some variables on the frequency of toxoplasmosis in the studied groups, such as age, age at diagnosis, contact with animals, residence and smoking were shown in Table 3.

Table 1: Seroprevalence of toxoplasmosis in studied subjects by ELISA test.[1]

Group	*Mean ± SE*	
	IgM (IU/mL)	*IgG (IU/mL)*
Patients with T2DM and Toxoplasmosis	2.096 ± 0.32 b	159.04 ± 12.32 b
Patients with T2DM	1.151 ± 0.17 c	5.58 ± 0.52 c
Patients with Toxoplasmosis	2.782 ± 0.11 a	206.41 ± 8.00 a
Controls	2.347 ± 0.11 ab	3.79 ± 0.72 c
LSD value	0.580 **	21.763 **
p-value	0.0001	0.0001

[1] ELISA was used for determination of anti-*T. gondii* IgG and anti-*T. gondii* IgM antibodies, Cut-off value: (positive ≥ 11.0 IU/mL), (negative < 9.0 IU/mL), equivocal (9.0–11.0 IU/mL), LSD= least significant difference. SE: standard error. ** (p ≤0.01). Means in the same column with different letters differed significantly. The highest mean takes the letter a and so on downward, and if you find a mean that takes two letters like ab, this does not differ neither from the mean that carries a nor from the mean that carries b.

Table 2: Frequency of *Toxoplasma* IgG antibodies in T2D patients and non-diabetic individuals by ELISA test.

Individuals		*Toxoplasma IgG Positive n (%)*	*Toxoplasma IgG Negative n (%)*	*Chi-square p-value*	*OR*	*95%Cl*
Diabetic n= (69)	Male	20 (29)	15 (21.7)	0.40[a]	-	
	Female	16 (23.1)	18 (26)		1.50	0.58-3.87
	Total	36 (52.1)	33 (47.9)			
Non diabetic n= (92)	Male	22 (23.9)	25 (27.1)	0.001[b]	-	
	Female	7 (7.6)	38 (41.3)		4.77	1.77-12.84
	Total	29 (31.5)	63 (68.4)	0.00008[c]		

a= comparison between male and female for infection in diabetic group, b=Comparison between male and female for infection in non-diabetic group, c= comparison of *T. gondii* IgG antibodies seropositivity between diabetic and non-diabetic individuals. OR: Odd ratio; 95% CI: Confidence interval.

Table 3: Effect of some variables on the frequency of infection with *T. gondii.*

Factor		*Patients with T2DM & Toxoplasmosis n= (36)*	*Patients with T2DM n= (33)*	*Patients with Toxoplasmosis n= (29)*	*Controls n= (63)*	p-value
Age		54.5 ± 1.95	54.84 ± 1.73	52.17 ± 1.16	53.38 ± 1.51	0.89
Age at diagnosis of diabetes		44.87 ± 1.60	44.82 ± 1.59	-----	----	0.91
Contact with animals	No	34 (94.44%)	26 (78.79%)	23 (79.32%)	61 (96.83%)	0.008
	Yes	2 (5.56%)	7 (21.21%)	6 (20.68%)	2 (3.17%)	
Residence	Urban	35 (97.22%)	31 (93.94%)	27 (93.10)	57 (90.47%)	0.641
	Rural	1 (2.78%)	2 (6.06%)	2 (6.9%)	6 (9.53%)	
Smoking	No	30 (83.3%)	29 (87.88%)	27 (93.10%)	57 (90.47%)	0.608
	Yes	6 (16.7%)	4 (12.12%)	2 (6.9%)	6 (9.53%)	

Data were expressed as counts with percentages in parentheses or mean ± SE.

Table 4: Comparison among different groups in BMI and Duration of diabetes.

Group	*Mean ± SE*	
	BMI (kg/m^2)	*Duration (year)*
Patients have T2DM & Toxoplasmosis	27.91 ± 0.63 **ab**	9.52 ± 1.63 **a**
Patients with T2DM	28.33 ± 0.70 **a**	10.02 ± 1.53 **a**
Patients with Toxoplasmosis	26.68 ± 029 **bc**	0.00 ± 0.00 **b**
Controls	26.08 ± 0.43 **c**	0.00 ± 0.00 **b**
LSD value	1.498 *	3.091 **
p-value	0.0125	0.0001

* (p≤0.05), ** (p≤0.01). Means in the same column with different letters differed significantly.

Non-significant differences were found in the age of subjects, age at diagnosis of T2DM, residence and smoking factors among studied groups. While a high significant difference (21.21%, p < 0.01) was found considering the contact

with animals' factor. Highly percentage of infection with toxoplasmosis in individuals with no contact with animals (Table 3), suggesting that other probable routes may cause the infection. Previous epidemiological studies have been reported similar findings.[34,35] Although cats are considered the definitive host of *T. gondii*, the lack of association with cats appears to be a minor risk factor compared to other risk factors such as contact with contaminated foods.[25] While data from other studies support cat contact as a risk factor, [36-38] and prevention of *T. gondii* infection through cat exposure may be possible because cats only shed oocysts 1–3 times in their lifetime.[28, 39]

In Table 4, a comparison among different groups in body mass index (BMI) revealed that there were significant differences between BMI means of controls (26.08 ± 0.43 c) and patients with T2DM with and without *Toxoplasma* latent infection (groups 1and 2) (27.91 ± 0.63 ab and 28.33 ± 0.70 a, respectively) while, there was no significant difference between controls and patient with latent toxoplasmosis (group 3) (BMI = 26.68 ± 029 bc), (LSD=1.498). Subsequently, this reveals that BMI is not considered a risk factor for toxoplasmosis and is only related to T2DM. This finding is in concordance with other studies excluded BMI as a risk factor for *T. gondii* infection[28,40] While, previous studies identified BMI as a factor for *T. gondii* infection.[10,20,21,25,31,39]

No significant difference was observed in the duration of diabetes between T2DM patients with toxoplasmosis (9.52 ± 1.63 years) and T2DM patients without toxoplasmosis (10.02 ± 1.53 years), (LSD= 3.09). This finding making the assumption that toxoplasmosis may be considered as a risk factor and pave the way for T2DM. On the other hand, diabetes may pave the way for toxoplasmosis depends on which one happened first. The high frequency of toxoplasmosis among diabetic patients supports this association.

CONCLUSION

We concluded that there is a strong association between T2DM and toxoplasmosis. Therefore, more attention should be pay to *T. gondii* infection due to high frequency of infection in T2DM patients. Contact with animals and BMI were not identified as risk factors for *T. gondii* infection. Further studies on larger sample size are needed to confirm the role of toxoplasmosis in patients with T2DM.

AUTHOR CONTRIBUTIONS

M. M. supervised the work. O. S. write the manuscript. A. A. supervised the process of patient's investigation. "All authors have read and agreed to the published version of the manuscript."

INSTITUTIONAL REVIEW BOARD STATEMENT

"The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) College of pharmacy/ University of Baghdad (protocol code 3102020C approved in September 2020.

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