

Investigating the potential link between seroprevalence of *Toxoplasma* IgG and both types of diabetes mellitus in Benha city, Egypt

Original
Article

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ABSTRACT

Background: In immunocompromised individuals, e.g. diabetics, toxoplasmosis is one of the significant opportunistic illnesses. The sensitivity and susceptibility to infections increases in diabetic patients causing severe health consequences unless diagnosed and treated early.

Objective: The study was performed to detect the possible association between toxoplasmosis and both types of diabetes mellitus linked with glycated hemoglobin (HbA1c) levels.

Patients and Methods: The study included 180 serum samples, 90 from diabetic patients and 90 healthy controls. Diabetic cases were divided into 22 diagnosed as type 1 diabetes (T1DM) and 68 type 2 diabetes (T2DM). Sera were tested for *Toxoplasma* IgG antibodies using ELISA technique, and HbA1c levels were estimated in all diabetic patients.

Results: *Toxoplasma* IgG seropositivity was recorded in 67/90 (74.4%) of diabetic patients and 30/90 (33.3%) of the controls with statistically significant difference ($P<0.05$). Among the diabetic patients, IgG seropositivity was recorded in 17/22 (77.3%) of T1DM cases, and 50/68 (73.5%) of T2DM cases. The difference between the two diabetic groups was statistically significant ($P<0.05$). A positive correlation was recorded between IgG seropositivity and HbA1c levels in both types of diabetes.

Conclusion: It is critical to identify and treat toxoplasmosis in diabetic patients in order to prevent serious outcomes due to the high prevalence of toxoplasmosis in diabetic patients compared to healthy individuals.

Keywords: diabetics; HbA1c; IgG seroprevalence; immunocompromised; toxoplasmosis.

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INTRODUCTION

Almost all warm-blooded animal species, including humans, are susceptible to infection by the obligate apicomplexan intracellular parasite *T. gondii*^[1]. Due to the severity of toxoplasmosis, its high incidence, and its possible prevention specially in immunocompromised patients, *T. gondii* was given priority by the Centers for Disease Control and Prevention as one of the top "Five Neglected Parasitic Infections"^[2]. Notably, *T. gondii* can be transmitted to humans by different means including ingestion of oocyst-contaminated food or water, consuming raw meat containing tissue cysts, vertical transmission from mother to fetus, organ transplantation, and blood transfusion^[3]. According to a relatively recent estimate, this parasite infects one-third of all humans on earth^[4]. Human populations are dead-end hosts for toxoplasmosis with up to 80% suffering from chronic asymptomatic infection^[5]. A previous systematic review article in Iran reported high *T. gondii* seroprevalence rates of more than 45% in a variety of

immunocompromised human groups, including HIV/AIDS patients, cancer patients, transplant recipients, and hemodialysis patients^[6].

Despite innate acute inflammatory responses and antigen-specific adaptive immunity, *T. gondii* can infect and multiply in any nucleated host cells, resulting in the generation of different inflammatory markers that promote a chronic inflammatory state^[7]. Numerous studies have shown a significant correlation between chronic *T. gondii* infection and various neurological conditions and malignancies. Additional autoimmune disorders include thyroid disease, systemic sclerosis, rheumatoid arthritis, and inflammatory bowel syndrome^[8-12].

Symptomatic toxoplasmosis is less common in immunocompetent individuals, but this does not prevent development of tissue cysts in asymptomatic infections. Toxoplasmosis in humans can be identified by isolation, serology, histology, molecular detection,

or a combination of these techniques. The infection has non-specific clinical symptoms that are insufficiently recognizable to provide a conclusive diagnosis. Antibody determination against *T. gondii* may help in diagnosing the state of infection. There are numerous commercially accessible serologic assays for diagnosis of toxoplasmosis^[8].

The 21st century's top public health threat is diabetes mellitus (DM) that affects more than one billion people globally; and by the year 2030, 552 million individuals, or 7.7% of the population, are predicted to be affected by DM^[13]. Diabetes is one of the most worldwide chronic diseases characterized by sustained hyperglycemia and associated with interruption of carbohydrate, fat and protein metabolism that result from abnormalities in insulin excretion or both conditions^[14]. Diabetic patients are predisposed to contracting toxoplasmosis due to suppression of their immune systems^[15]. Hyperglycemia caused by abnormalities in insulin hormone release characterizes T1DM, while the improper response to insulin is a hallmark of T2DM^[13]. Since T1DM is regarded as an autoimmune condition, genetic and environmental factors are likely to be involved^[13]. Enteroviruses were also associated with T1DM^[16].

A new area of research called toxoplasmic T2DM may be initiated as a result of *T. gondii* latent infections^[17]. Toxoplasmosis and both types of diabetes were strongly linked^[18]. Diabetic patients are more susceptible to medical problems and infectious manifestations with greater severity^[19]. The prevention and control of toxoplasmic complications can greatly benefit from an early and precise diagnosis, especially in those who are at risk. In our study we chose to conduct a matched case-control study in Benha city to assess *T. gondii* seropositivity link to both types of diabetes mellitus.

PATIENTS AND METHODS

This case-control study was performed on patients attending outpatient clinics of Benha University and Benha Teaching Hospitals from September 2021 to January 2022.

Study design: To detect the possible association between toxoplasmosis and both types of DM, blood samples from diabetic patients and controls were collected for estimation of HbA1c levels and *Toxoplasma* IgG seropositivity. Diabetic cases were divided into type 1 and type 2 diabetes.

Target population: The study included 180 individuals; 90 diabetic patients and 90 healthy nondiabetic volunteers in whom fasting and post-prandial blood glucose levels were below the typical diabetic criteria. Immunosuppressive medication

recipients and diabetic patients with other metabolic syndrome conditions were not included in this study. Since there is an association between toxoplasmosis and metabolic problems, such as hypertension, hypertriglyceridemia and hypercholesterolemia, the study focused on patients afflicted only with diabetes excluding those suffering from any of these disorders.

Questionnaire: Each participant filled out a structured questionnaire that contained inquiries about their age, gender, residence, contact with cats, source of water, consumption of raw vegetables, and consumption of raw or undercooked meat; or history of any of the metabolic syndrome conditions.

Sampling and serological assay: Blood samples were collected from diabetic patients with history of diabetes and receiving antidiabetic treatment and non-diabetic controls. Samples were sent to the Laboratory of Clinical Pathology Department, Benha Faculty of Medicine for evaluation of HbA1c levels. Blood samples (2-3 ml) were centrifuged, and sera were frozen at -20°C for testing *Toxoplasma* IgG antibodies by the enzyme linked immunoassay (ELISA) technique. The kits were provided by Acon, USA. The ELISA procedure was conducted according to the manufacturer's instructions^[20].

Statistical analysis: The program used was SPSS version 26. Quantitative data were analyzed using mean and standard deviation, while frequency and percentage were used with qualitative data. Chi square test and Fischer exact test to compare frequencies and analysis of variance (ANOVA) with post hoc test (LSD) were used to compare means. Pearson correlation was applied for the relationship between IgG titer and HbA1c. Significance was considered if P value ≤ 0.05 .

Ethical considerations: Participants were informed about the purpose of the study and provided their consent. All participants agreed to share in accordance with the ethical norms and informed with the study results.

RESULTS

Our study findings showed that total *Toxoplasma* IgG total seropositivity was 97/180 (53.9%) in the group understudy, constituting 67/90 (74.4%) of all diabetic cases, and 30/90 (33.3%) of the healthy controls with statistically significant difference ($P < 0.05$). Among the diabetic patients, *Toxoplasma* seropositivity in T1DM was 17/22 (77.3%) and in T2DM it was 50/68 (73.5%) with no statistically significant difference ($P > 0.05$) (Table 1).

Higher HbA1c levels (>7) were detected in 8/17 (47.1%) of T1DM patients and 15/50 (30%) of T2DM patients who had toxoplasmosis. A statistically

Table 1. Comparison of *Toxoplasma* IgG seropositivity in the studied diabetic cases and controls.

	Diabetic cases	Controls	Total	Statistical analysis		
	(n= 90) No. (%)	(n= 90) No. (%)	(n= 180) No. (%)	Odds ratio (95% CI)	X ² test	P value
<i>Toxoplasma</i> IgG						
Positive	67 (74.4)	30 (33.3)	97 (53.9)	5.83 (3.06-11.11)	30.61	<0.001*
Negative	23 (25.6)	60 (66.7)	83 (46.1)			
	T1DM (n= 22) No. (%)	T2DM (n= 68) No. (%)	Total (n= 90) No. (%)			
<i>Toxoplasma</i> IgG						
Positive	17 (77.3%)	50 (73.5%)	67 (74.4%)	NA	0.122	0.73
Negative	5 (22.7%)	18 (26.5)	23 (25.6%)			

CI: Coefficient interval; NA: Not applicable; *: Significant ($P \leq 0.05$).

significant difference was found between IgG seropositivity and both types of diabetes in relation to mean value of HbA1c level (7.64±1.37 in T1DM, and 8±1.18 in T2DM) ($P \leq 0.05$) (Table 2). Additionally,

there was an insignificant positive correlation between *Toxoplasma* IgG and HbA1c among both groups of diabetes ($r=0.239$, $P \leq 0.05$ T1DM) ($r=0.160$, $P \leq 0.05$ T2DM) (Table 3).

Table 2. Relation between *Toxoplasma* IgG seroprevalence and HbA1c level.

HbA1c	T1DM (22)			P value	T2DM (No. = 68)		
	Positive IgG (17)	Negative IgG (5)	P value		Positive IgG (50)	Negative IgG (18)	P value
	No. (%)	No. (%)			No. (%)	No. (%)	
>7	8 (47.1)	5 (100)	0.054	15 (30)	12 (66.7)	0.006*	
≤7	9 (52.9)	0 (0)		35 (70)	6 (33.7)		
Mean ± SD	7.64 ± 1.37	6.48 ± 0.43	0.035*	8.0 ± 1.18	7.13 ± 1.23	0.006*	
Range	6.0 - 11.0	6.0 - 6.9		6.0 - 11.0	6.0 - 10.5		

*: Significant ($P < 0.05$)

Table 3. Correlation between *Toxoplasma* IgG and HbA1c among both T1DM and T2DM cases.

	IgG	r	P value
HbA1c	T1DM	0.239	0.284
	T2DM	0.160	0.193

Patients with T1DM: The mean age of T1DM with *Toxoplasma* IgG positivity was 45.94±13.4 with age range of 22-70 years. There was no significant difference between T1DM female patients (64.7%) and males (35.3%). The seroprevalence of *T. gondii* was higher in T1DM patients living in rural areas (70.6%) compared to those in urban areas (29.4%) with no statistically significant difference. Regarding to risk factors of toxoplasmosis, a significantly seroprevalence of *T. gondii* was found in relation to previous consumption of undercooked meat, the source of the drinking water and contact with cats ($P3 \leq 0.05$) (Table 4).

Patients with T2DM: IgG positive T2DM cases had 61.1±10.4 mean age with a range of 36-85 years with

statistically significant difference ($P4 \leq 0.05$). No significant difference was observed regarding gender or residence. In T2DM patients, 60% living in rural areas were seropositive for *T. gondii*, while in urban regions 40 % were IgG-positive which was nonsignificant. *T. gondii* seroprevalence was not substantially different among T1DM patients based on eating raw meat, or cat contact. There was a significant association ($P4 \leq 0.05$) between IgG seroprevalence and both drinking water source and consumption of unwashed fruits or vegetables (Table 4).

A statistical significance was found between all studied groups regarding age, consumption of unwashed vegetables or fruits, drinking water source, consumption of undercooked meat and cat contact ($P1 \leq 0.05$). Furthermore, a significant variation was detected between diabetic group (T1DM+T2DM) and control in relation to drinking water source and consumption of unwashed vegetables or fruits ($P2 \leq 0.05$) (Table 4).

Table 4. Relation between IgG seropositivity and socio-demographic data in the studied groups (T1DM, T2DM and control).

Variables	T1DM (22)		T2DM (68)		Control group (90)		Statistical analysis			
	Positive	Negative	Positive	Negative	Positive	Negative	P1	P2	P3	P4
	IgG (17)	IgG (5)	IgG (50)	IgG (18)	IgG (30)	IgG (30)				
Age										
Mean ±SD	45.94±13.4	52.4±8.44	61.1±10.4	56.94±12.63	49.63±15.41	54.78±15.62	<0.001*	0.071	0.339	<0.001*
Range	22.0-70.0	42.0-60.0	36.0-85.0	24.0-72.0	30.0-77.0	28.0-77.0				
Sex										
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	P1	P2	P3	P4
Male	6 (35.3)	3 (60.0)	17 (34.0)	7 (38.9)	11 (36.7)	26 (43.3)	0.97	0.82	0.93	0.81
Female	11 (64.7)	2 (40.0)	33 (66.0)	11 (61.1)	19 (63.3)	34 (56.7)				
Residence										
Rural	12 (70.6)	5 (100.0)	30 (60.0)	8 (44.4)	22 (73.3)	35 (58.3)	0.43	0.31	1.0	0.23
Urban	5 (29.4)	0 (0.0)	20 (40.0)	10 (55.6)	8 (26.7)	25 (41.7)				
CVF®										
Yes	4 (23.5)	1 (20.0)	11 (22.0)	4 (22.2)	1 (3.3)	5 (8.3)	0.04*	0.019*	0.051	0.026*
No	13 (76.5)	4 (80.0)	39 (78.0)	14 (77.8)	29 (96.7)	55 (91.7)				
UCM#										
Yes	5 (29.4)	1 (20.0)	3 (6.0)	3 (16.7)	1 (3.3)	9 (15.0)	0.016*	0.27	0.018*	1.0
No	12 (70.6)	4 (80.0)	47 (94.0)	15 (83.3)	29 (96.7)	51 (85.0)				
Water source										
Yes	3 (17.6)	1 (20.0)	0 (0.0)	0 (0.0)	28 (93.3)	56 (93.3)	<0.001*	<0.001*	<0.001*	<0.001*
No	14 (82.4)	4 (80.0)	50 (100.0)	18 (100.0)	2 (6.7)	4 (6.7)				
Cat contact										
Yes	6 (35.3)	1 (20.0)	2 (4.0)	1 (5.6)	1 (3.3)	6 (10.0)	0.002*	0.27	0.006*	1.0
No	11 (64.7)	4 (80.0)	48 (96.0)	17 (94.4)	29 (96.7)	54 (90.0)				

®: Ingestion of contaminated vegetables or fruits; #: Ingestion of undercooked meat; *: Significant (P<0.05); **P1**: Significance between all groups; **P2**: Significance between both types of diabetes and control; **P3**: Significance between control and T1DM; **P4**: Significance between control and T2DM.

DISCUSSION

An emerging field of research is starting to examine the association of infectious and environmental pathogens with diabetes. There is still debate on the relationship between toxoplasmosis and diabetes mellitus, with some studies yielding contradictory findings^[21]. Our research was conducted to update our knowledge regarding potential links between *T. gondii* and T1DM and T2DM in our locality. Our study findings showed that diabetic cases had significantly higher anti-

Toxoplasma IgG in their serum than the non-diabetic controls (74.4% versus 33.3%) (P<0.001). *Toxoplasma* seropositivity was found to be 77.3% in T1DM and 73.5% in T2DM. Our results support the notion that both types of diabetes and chronic toxoplasmosis are related since anti-*Toxoplasma* IgG seroprevalence was considerably greater in T1DM and T2DM patients than in the healthy non-diabetic control group. Our findings corroborate a previous study conducted in Egypt in 2018 by Hemida *et al.*^[22] which showed that

diabetic patients had higher seropositivity levels for anti-*Toxoplasma* antibodies than non-diabetic patients. (*Toxoplasma* IgG was 46% versus 24%, respectively). Saheb^[23] also pointed out that diabetic patients exhibited higher *T. gondii* IgG-Ab positive levels when compared to healthy controls. This conclusion is also supported by a different Iranian investigation^[24].

Since several infectious disorders have been connected to T1DM, it has been observed that T1DM patients are more likely to contract toxoplasmosis^[17]. Additionally, *T. gondii* can infect all nucleated cells including pancreatic insulin secreting cells, T1DM development could result from any defect in insulin synthesis. Consequently, T1DM could be brought on by toxoplasmosis^[25-27]. The two theories support the association between T1DM and toxoplasmosis. Due to weakened immune system, T2DM patients are more vulnerable to infections like toxoplasmosis^[16]. This finding was in agreement with Goekce *et al.*^[28] who observed that *T. gondii* IgG seropositivity in T1DM patients was considerably higher than in controls (56.62 % versus 22.4%). Asgari *et al.*^[29] also reported a higher prevalence of toxoplasmosis in type I diabetes patients compared to nondiabetic controls. Beshay *et al.*^[26] stated that anti-*Toxoplasma* IgG was positive in 86.37% of T1DM patients (GI), 66.67% of T2D patients (GII) and 60% in the control group (GIII). The seropositivity of anti-*T. gondii* IgG was significantly higher in T1D (GI) when it was compared to T2D (GII) or the control group (GIII). With the same concept, Molan and Ismail^[30] observed that 33.4% of the seemingly healthy persons (control group) were seropositive for anti-*Toxoplasma* IgG, compared to 75.3% of T1DM patients and 65.1% of T2DM patients. Ozelik *et al.*^[31] discovered that T2DM patients had a two-fold increased risk of toxoplasmosis infection compared to healthy controls and so did Younis *et al.*^[32]. Conversely, Siyatpanah *et al.*^[33] and Khalili *et al.*^[34] showed that there was no statistically significant difference between the incidence of toxoplasmosis in diabetes and nondiabetic people. A case-control research in a Mexican population conducted in 2017 also found no correlation between toxoplasmosis and diabetes^[35].

Regarding sociodemographic parameters examined in this study, there was no statistically significant difference between T1DM cases. The mean age of the study population was 45.94±13.4 in T1DM and 61.1±10.4 in T2DM with significant variation in T2DM. Whereas, sex and residence were insignificant parameters. The increase in the mean age of *Toxoplasma* seropositive diabetic patients could be due to increase of life expectancy with increasing possibility of contact with one of the transmission routes^[36,37]. The prevalence of toxoplasmosis also tended to increase with age, according to Shin *et al.*^[38], although this increase was not statistically significant. Hemida *et al.*^[22] discovered, however, that there was no statistically significant

link between seropositivity and ageing. Concerning toxoplasmosis risk factors there was a significant difference between IgG seroprevalence and previous consumption of undercooked meat, the source of the drinking water and contact with cats in T1DM ($P \leq 0.05$); while both water source and consumption of unwashed fruits or vegetables were of significant variation in T2DM ($P \leq 0.05$). The majority of this study participants were living in rural areas with a simple unhygienic lifestyle resulting in greater risk of exposure to infection. It is possible that cats' sporulated oocysts, which can remain infectious for several months and even longer than a year, are polluting the soil and sand^[39]. Two studies^[40,41] demonstrated a strong correlation between ingesting unwashed or raw fruits and vegetables and *T. gondii* seroconversion. This mode of infection may be the origin of *Toxoplasma* infection in vegetarians and herbivores^[37,42]. Studies by Stull *et al.*^[43], and Kravetz and Federman^[44] highlighted the importance of cats as the disease's most likely source of transmission. Besides, the handling and ingestion of raw or undercooked meat was recognized as a source of toxoplasmosis by epidemiological studies and in a number of outbreaks^[45-47].

In our research, 47.1% of T1DM patients with toxoplasmosis had uncontrolled diabetes (higher HbA1c values >7), with HbA1c mean value of 7.64±1.37 with statistical significance ($P \leq 0.05$). *Toxoplasma*-infected T2DM patients exhibited higher HbA1c values (>7) with a statistically significant mean (7.98 ±1.18) ($P \leq 0.05$). According to the rise in HbA1c, immunoglobulin glycation occurs in diabetic individuals, that may impair the biological function of the antibodies hence increasing their vulnerability to infections^[48]. Our currently conducted research revealed that there was a positive correlation between *Toxoplasma* IgG and HbA1c among both T1DM and T2DM. Our results were in accordance with Qudus *et al.*^[49] who found that HbA1c was high in diabetic patients infected with *T. gondii*. Another study^[22] reported that the correlation of IgG anti-*Toxoplasma* antibodies results with HbA1c of the patient group was irrelevant. According to a large scale cohort study conducted to identify infection risk among type 1 and type 2 diabetic patients, the investigators concluded that poor glycemic control was strongly associated with serious infection, and should be given high priority. Additionally, Abdullah *et al.*^[21] indicated that diabetic patients with high HbA1c were at high risk for postoperative wound infection. Our results also agreed with those of Abdul *et al.*^[51], Jang *et al.*^[52] and Mohapatra *et al.*^[53]. Nowadays, HbA1c is used as a critical indicator of insufficient glycemic control, increasing the susceptibility of diabetics to infection^[54].

In conclusion, the outcome data showed a substantial correlation between chronic toxoplasmosis infection and both T1DM and T2DM, although there are still many unanswered issues about the precise

mechanisms of *T. gondii* in the pathogenesis of DM, particularly T1DM. The precise relationship between *T. gondii* and DM has to be clarified by additional research.

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