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Seroepidemiology of *Toxoplasma gondii* infection in diabetic patients and the impact of toxoplasmosis on diabetes associated complications in Minia city, Egypt

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ABSTRACT:

— ***Objective:*** The correlation between both types of diabetes and toxoplasmosis has not been firmly established. To confirm this correlation, we conducted this study to determine the seroprevalence of toxoplasmosis and to identify possible associated risk factors in diabetic patients.

— ***Patients and Methods:*** The seroprevalence of IgG and IgM antibodies to *Toxoplasma gondii* was assessed in a cohort study that included 300 diabetic patients (150 Type 1 diabetes mellitus patients and 150 Type 2) in addition to 300 healthy controls. A structured questionnaire was used to collect sociodemographic data to identify the risk factors for seropositive diabetic cases.

— ***Results:*** The total seroprevalence of *Toxoplasma gondii* antibodies was significantly higher in diabetic patients of both types ($p<0.0001$) than in healthy control individuals. Recent *Toxoplasma gondii* infection was clearly observed in type 2 diabetic patients. Female diabetic patients (71.1%) were found to be more susceptible to *Toxoplasma gondii* infection. Also, living in rural areas (75.6%), illiteracy (46.7%), consuming raw vegetables (91.1%), and contact with soil (68.9%) were found to be the most significant risk factors for toxoplasmosis in diabetic patients. Furthermore, 42.2% of positive *Toxoplasma gondii* diabetic cases showed diabetic complications.

— ***Conclusions:*** There is a significant association between *Toxoplasma gondii* infection and diabetes; also, *Toxoplasma gondii* could be a potential cause of diabetes. Moreover, type 2 diabetes mellitus patients are more susceptible to acquiring *Toxoplasma gondii* infections, and this infection could be a risk factor for diabetes complications.

— ***Keywords:*** Toxoplasma gondii, *Diabetic patients, IgM, IgG, Risk factors.*

INTRODUCTION

Toxoplasma gondii (T. gondii) is an obligate intracellular parasite that induces infection in most mammals and birds. Humans get infected with *T. gondii* through the intake of food contaminated with *T. gondii* oocysts found in cat feces or *T. gondii* animal tissue cysts containing bradyzoites[1]. Toxoplasmosis can be transmitted *via* a variety of routes, including the placental route, blood transfusion, and tissue transplantation[2,3].

Toxoplasmosis is an asymptomatic infection in healthy individuals, but in immunocompromised individuals due to malignant diseases, immunosuppressive treatment, corticosteroids, splenectomy, and radiotherapy, *T. gondii* reactivates and causes a life-threatening disease[4]. Diabetes mellitus (DM) is a group of metabolic disorders

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that affects about half a billion people worldwide. DM is characterized by a high blood glucose level due to insulin resistance, insulin production insufficiency, or increased glucagon hormone production. Type 1 diabetes (T1DM) is an autoimmune disease, while Type 2 diabetes (T2DM) results from an improper response to insulin[5,6].

DM is now an increasing health issue in Egypt due to many factors: increasing central obesity, lifestyle, changing food habits, and increasing hepatitis C infection[7].

DM has a negative effect on innate cellular immunity, and microorganisms have a greater ability to adhere to diabetic cells. Moreover, the virulence of some microorganisms increases in a high-glucose environment, which makes diabetic individuals more susceptible to infections[8]. Consequently, diabetic patients are predisposed to contracting toxoplasmosis due to the suppression of their immune systems[9]. Also, Kankova et al[10] found that pregnant women with chronic toxoplasmosis had increased blood glucose levels during the oral glucose tolerance test and a higher prevalence of gestational diabetes mellitus in the 24-28th gestational weeks compared to non-infected women.

Additionally, a few studies[11-13] in Egypt have revealed higher anti-*T. gondii* antibodies in diabetic patients (especially T1DM) than in non-diabetic patients, and these studies have revealed a causal link between *T. gondii* infection and type 1 diabetes.

However, some global studies[14] on the relationship between toxoplasmosis and diabetes have been conducted, and the results of these studies have been controversial.

So far, the correlation between both types of diabetes and toxoplasmosis has not been firmly established in literature, and to confirm this correlation, we conducted this study to determine the seroprevalence of toxoplasmosis and to identify possible associated risk factors in diabetic patients. Furthermore, we investigated a possible link between toxoplasmosis and diabetes complications in Minia, Egypt.

PATIENTS AND METHODS

Study Population and Design

An age, gender, and residence-matched cohort study was carried out on 300 diabetic patients (150 T1DM and 150 T2DM) referred to the Tropical Medicine and Gastroenterology Outpatient Clinic, Faculty of Medicine, Minia University, between December 2022 and February 2023. In addition, 300 nondiabetic subjects were recruited as a control group. DM patients were excluded from the control group by history taking and measuring their random blood sugar.

Inclusion criteria in T1DM were based on the age of onset, family history, presence of serum autoantibodies [glutamic acid decarboxylase (GAD) antibody, islet cell antibody (ICA) and insulin autoantibody], serum insulin level, and ketoacidosis. Inclusion criteria for T2DM patients included diabetes symptoms (thirst, polydipsia, polyuria, weight loss), a fasting plasma glucose level ≥ 126 mg/dL (≥ 7.0 mmol/L), and/or the 2-h value in 75 g oral glucose tolerance test (OGTT) ≥ 200 mg/dL (≥ 11.1 mmol/L), and/or random plasma glucose level ≥ 200 mg/dL[15].

The patients and the control subjects were interviewed using a questionnaire containing all sociodemographic data and possible toxoplasmosis risk factors. Diabetic complications (renal diseases and ocular manifestations) were also recorded for diabetic patients.

Serology

Venous blood samples (5 mL) were collected under aseptic precautions using sterile disposable syringes. The blood samples were immediately transported to the Laboratory of Parasitology Department, Minia University, and these samples were centrifuged at 3,000 rpm for 5 min. Sera were separated and kept in labeled sterile microtubes at -20°C until further processing. Each serum sample was tested for the presence of anti- *T. gondii* antibodies IgG and IgM using a commercial ELISA kit (Genesis Diagnostics, Cat # GD080, UK) following the manufacturer's instructions. The positive titer was > 10 IU/ mL. The clinical specificity and sensitivity of the IgM kits were 99% and 100%, respectively. The clinical specificity and sensitivity of the IgG kits were 99% and 98%, respectively.

Ethical Consideration

The study protocol was approved by the Ethics Committee of the Department of Medical Parasitology and the Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Minia University, at their monthly meeting in December 2022 and the Institutional Committee of Research Ethics, Faculty of Medicine, Minia University, Egypt, gave its approval (No. 568-2022). An informed written consent was obtained from each participant after explaining the purpose and procedures of this study.

Statistical Analysis

All analyses were performed using SPSS, version 25 (IBM Corp., Armonk, NY, USA). Quantitative data were presented by mean (standard deviation), while qualitative data were presented by frequency distribution. The Chi-square test was used to compare the proportions. Independent sample *t*-test was used to compare between means. The probability of less than 0.05 was used as a cut-off point for all significant tests, and all statistical tests were 2-tailed.

RESULTS

The overall seroprevalence of *T. gondii* infection in diabetic patients and control subjects was 75% (225/300) and 33.3% (100/300), respectively (p<0.0001). Of these, IgG antibodies of *T. gondii* were found in 205

(86.3%) out of 300 diabetic patients and in 100 (33.3%) out of 300 control subjects (p<0.0001). 135 (45%) diabetic patients and 30 (10%) controls were positive for IgM antibodies to *T. gondii* (p<0.0001). Also, the prevalence of IgG antibody levels was 53.3% and 83.3% in T1DM and T2DM, respectively. Moreover, IgM antibody level was 30% and 60% in T1DM and T2DM, respectively. This seropositivity was statistically significant for IgM and IgG among diabetic patients of both types compared to controls (p<0.0001), as shown in Table 1. Socio-demographic characteristics and clinical data of diabetic patients, including age, gender, educational level, area of residence, consumption of undercooked meat, consumption of raw vegetables, contact with soil, contact with cats, HbA1c level, and complications of diabetes, are shown in Table 2. The mean age of diabetic patients was 51.21±7.47 years. Female diabetic patients (71.1%) had a significantly higher seropositivity for *T. gondii* than male diabetic patients (28.9%) (p<0.0001). Rural area residents (75.6%) had a higher significant *T. gondii* seroprevalence compared to urban area residents (24.4%) (p<0.0001). Illiterate patients (46.7%) had a higher seroprevalence than the educated ones (28.9%), and this was statistically significant (p<0.0001). Diabetic patients consuming raw vegetables and who are more in contact with soil had significantly higher seropositivity compared to others (91.1% and 68.9%, respectively) (p<0.0001). HbA1c had a significant level in the seropositive diabetic patients (p=0.04). Finally, complications in diabetic patients were significant in the seropositive patient for *T. gondii* (p=0.03). However, the consumption of undercooked meat and cat contact showed no statistically significant difference between the seropositive and seronegative diabetic patients.

Regarding type of diabetes, there was a significant difference in the prevalence of complications between type 2 and type 1 diabetic patients; 77.1% of T2DM have complications compared to 46.7% in T1DM. Meanwhile, there was not a significant relationship between T1DM and T2DM regarding gender, residence, educational level, consumption of undercooked meat, consumption of raw vegetables, contact with soil, contact with cat, and glucose level (Hb A1c), as shown in Table 3.

DISCUSSION

The relationship between DM and toxoplasmosis is still controversial, and to define this relation, many studies with diverse populations and communities are needed.

This research was conducted in Minia, Egypt, to determine this association among diabetic patients. The overall seroprevalence of *T. gondii* antibodies was significantly higher in diabetic patients of both types (p<0.0001) than the healthy control individuals, and this agreed with Hemida et al[12], Li et al[16], and Elkholy et al[17] while disagreed with Alvarado-Esquivel et al[18] who found no association between *T. gondii* infection and diabetes mellitus in Durango City, Mexico.

This higher seropositivity of toxoplasmosis in diabetic patients may be due to an increased susceptibility of these patients to many infections[8].

In this paper, the number of *T. gondii*-infected patients was higher among T2DM patients than that among T1DM patients, which was explained by a meta-analysis study done by Majidiani et al[19], who stated that T2DM patients are more susceptible to *T. gondii* infection and, chronic toxoplasmosis is a possible risk factor for T2DM and not for T1DM.

Moreover, T1DM patients were treated with insulin, which was suggested to protect against infections as an anti-hyperglycemic treatment that enhances the immune response of patients[20]; this also may explain why IgM seroprevalence (recent infection) was lower among patients with T1DM (30%) than among T2DM patients (60%) who were tested in this study.

Additionally, chronic toxoplasmosis was more associated with T2DM patients, as *T. gondii* IgG antibody seroprevalence among T2DM patients (83.3%) was higher than among T1DM patients (53.3%) and control group (33.3%). The possible suggested mechanism that explained why T2DM patients had higher IgG seroprevalence was that *T. gondii* infection might be a possible risk factor for T2DM by inducing inflammatory damage to pancreatic β cells and reducing β cell number, which in turn affects insulin production[21].

Moreover, the highest percentage of both IgG and IgM-positive patients was also among T2DM individuals (93.3%), and this data proved that T2DM patients are at higher risk for toxoplasmosis than T1DM patients (56.6%).

Table 1. Seropositivity of the anti-*Toxoplasma gondii* Abs in Diabetic patients (T1D and T2D) and Non-diabetic subjects (Control group).

	Diabetic patients		Non-diabetic subject (n=300)	*p*-value (T1D *vs.* Non-diabetic)	*p*-value (T2D *vs.* Non-diabetic)	*p*-value (Diabetic *vs.* Non-diabetic)
	T1DM (n=150)	T2DM (n=150)				
IgM[a] (%)	45 (30%)	90 (60%)	30 (10%)	<0.0001*	<0.0001*	<0.0001*
IgG[b] (%)	80 (53.3%)	125 (83.3%)	100 (33.3%)	<0.0001*	<0.0001*	<0.0001*
Total No. of positive cases	**85 (56.6%)**	**140 (93.3%)**	**100 (33.3%)**	**<0.0001***	**<0.0001***	**<0.0001***

[a]IgM positive (IgM+ combined IgM and IgG).
[b]IgG positive (IgG+ combined IgM and IgG).
p-value was calculated by using the Chi-square test. *Significant level of *p*-value is < 0.05.

Table 2. The correlation of some sociodemographic characteristics and clinical data and *Toxoplasma gondii* seropositivity in diabetic patients.

Variables	Diabetic patients		χ^2	*p*-value (positive *vs.* negative)
	Anti-*Toxoplasma gondii* Abs seropositivity			
	No. of positive *T. gondii* Abs (%) (n=225)	No. of negative *T. gondii* Abs (%) (n=75)		
Age:				
Mean ±SD	51.21 ± 7.47	53.50 ± 2.74		0.4
Gender:				
Male	65 (28.9%)	50 (66.7%)	32.38 (1)	<0.0001*
Female	160 (71.1%)	25 (33.3%)		
Residence:				
Rural	170 (75.6%)	15 (20%)	72.11 (1)	<0.0001*
Urban	55 (24.4%)	60 (80%)		
Education level:				
Illiterate	105 (46.7%)	5 (6.7%)	76.77 (2)	<0.0001*
Can read	55 (24.4%)	5 (6.7%)		
Educated	65 (28.9%)	65 (86.6%)		
Consumption of under-cooked meat:				
Yes	15 (6.7%)	10 (13.3%)	2.46 (1)	0.1
No	210 (93.3%)	65 (86.7%)		
Consumption of raw vegetables:				
Yes	205 (91.1%)	25 (33.3%)	101.76 (1)	<0.0001*
No	20 (8.9%)	50 (66.7%)		
Contact with soil:				
Yes	155 (68.9%)	10 (13.3%)	67.92 (1)	<0.0001*
No	70 (31.1%)	65 (86.7%)		
Contact with cats:				
Yes	111 (49.3%)	45 (60%)	4.55 (1)	0.1
No	114 (50.7 %)	30 (40%)		
Glucose level (Hb A1c)				
≤ 7	45 (20%)	23 (30.7%)	2.76 (2)	0.04*
> 7	180 (80%)	52 (69.3%)		
Complication of DM				
Yes	163 (72.4%)	44 (58.7%)	4.37 (1)	0.03*
No	62 (27.6%)	31 (41.3%)		

*Significant level of *p*-value is < 0.05. *p*-value was calculated by using the Chi-square test for qualitative values and an independent sample *t*-test for quantitative values.

The most stated risk factors for *T. gondii* infection are age, gender, residence, education, consumption of raw meat, consumption of raw vegetables, soil contact, cat contacts[22], glucose level (HbA1c)[17], and diabetic complications[23].

In the current study, there was a non-significant association between the age of the diabetic patients and the seroprevalence of *T. gondii* (p=0.4), and these results were consistent with Khattab et al[11]. The reason might be due to the high contact of an individual with one of the transmission routes[24,25]. Similarly, Shin et al[26] and Hemida et al[27] reported that the prevalence of toxoplasmosis was not statistically significant in relation to age.

In the present study, the seroprevalence of *T. gondii* infection was higher among female diabetic (71.1%) patients than among males (28.9%). Patients and toxoplasmosis seroprevalence can vary according to populations and their habits[28,29].

The seroprevalence of *T. gondii* in diabetic patients living in rural areas (75.6%) was higher than that of diabetic patients living in urban areas (24.4%) (p<0.0001). This data agreed with Gao et al[30].

The lifestyle of the residents of rural areas, poor sanitary conditions, and contact with domestic animals can highly explain this significant seroprevalence[30]. Also, it can be explained by the fact that cats' sporulated oocysts pollute the soil, and these oocysts can be infectious for several months or even longer than a year[31].

Table 3. The correlation of some sociodemographic characters and clinical data and *Toxoplasma gondii* seropositivity in T1DM and T2DM diabetic patients.

Variables	Diabetic patients		*p*-value
	Anti-*Toxoplasma gondii* Abs seropositivity (n= 225)		
	T1DM (n= 85)	T2DM (n=140)	
Age:			
Mean±SD	19.28 ±1.74	55.1 ±5.32	<0.0001*
Gender:			
Male	25 (29.4%)	40 (28.6%)	0.8
Female	60 (70.6%)	100 (71.4%)	
Residence:			
Rural	70 (82.4%)	100 (71.4%)	0.06
Urban	15 (17.6%)	40 (28.6%)	
Education level:			
Illiterate	35 (41.2%)	70 (50%)	0.2
Can read	25 (29.4%)	30 (21.4%)	
Educated	25 (29.4%)	40 (28.6%)	
Consumption of under-cooked meat:			
Yes	5 (5.9%)	10 (7.1%)	0.7
No	80 (94.1%)	130 (92.9%)	
Consumption of raw vegetables:			
Yes	80 (94.1%)	125 (89.3%)	0.2
No	5 (5.9%)	15 (10.7%)	
Contact with soil:			
Yes	65 (76.5%)	90 (64.3%)	0.05
No	20 (23.5%)	50 (35.7%)	
Contact with cats:			
Yes	41 (48.2%)	70 (50%)	0.7
No	44 (51.8%)	70 (50%)	
Glucose level (Hb A1c)			
≤ 7	15 (17.6%)	30 (21.4%)	0.4
> 7	70 (82.4%)	110 (78.6%)	
Complication of DM			
Yes	55 (64.7%)	108 (77.1%)	0.04*
No	30 (35.3%)	32 (22.9%)	

*Significant level of *p*-value is < 0.05. **p*-value was calculated by using the Chi-square test for qualitative values and an independent sample *t*-test for quantitative values.

Furthermore, our data showed a significant association between illiteracy (46.7%) and *T. gondii* seropositivity in diabetic patients. This is consistent with our previously published data (Kamal et al[22]).

In this study, there was a non-significant association between *T. gondii* infection and the consumption of undercooked meat by diabetic patients. However, this was in contrast to other studies[22,32], which stated that the consumption of undercooked meat was a significant *T. gondii* risk factor as most of Egyptians tend to consume some traditional undercooked beef food.

Consumption of raw vegetables (91.1%) and soil contact (68.9%) were also significantly associated risk factors for *T. gondii* infection in diabetic patients. The roles of raw vegetable consumption and soil contact in *T. gondii* infection were proven by many previous studies[16,22]. Also, Spalding et al[25] and Jones et al[33] reported that this mode of infection is possibly responsible for *Toxoplasma* infection in vegetarians and herbivores.

Moreover, our data demonstrated a non-significant association between *T. gondii* infection and cat contact, and this agreed with our previous data[22] and with Wei et al[34], who found a non-significant association between close cat contact and no cat contact and pointed out that cat contact may not be an important risk factor for *T. gondii* infection. In contrast, other researchers[16] have found a significant association between cat contact and *T. gondii* infection.

In the current study, the seropositivity for toxoplasmosis was higher in the uncontrolled diabetic group (HbAIc >7) (80%) than in controlled diabetic patients (HbA1c ≤7) (20%), and this was statistically significant. This was in agreement with Elkholy et al[17] and Qudus et al[35]. This finding may be due to immunoglobulin glycation occurring in diabetic individuals, which may impair the biological function of the antibodies, hence increasing their vulnerability to infections[36].

Diabetic patients are at greater risk of developing microvascular and macrovascular complications due to chronic, longstanding hyperglycemia and oxidative stress[37]. In this study, the potential association between *T. gondii* infection and diabetes complications was also examined among all diabetic patients. Of all diabetic seropositive patients, about 72.4% of cases have diabetic complications; this was statistically significant (p=0.03). These data agreed with Han et al[23], who stated that *T. gondii* might be a risk factor for developing complications in diabetic patients. On the other hand, these data were incompatible with Mohamed et al[38], who found no relation between toxoplasmosis and diabetic complications.

We suggested that *T. gondii* infection can elevate oxidative stress and enhance the development of diabetes' complications[39,40].

CONCLUSIONS

Our study concludes that there is a significant association between *T. gondii* infection and diabetes, also *T. gondii* could be a potential cause of diabetes. Moreover, T2DM patients are more susceptible to acquire *T. gondii* infections, and this infection could be a risk factor for diabetes' complications. Female diabetic patients are more susceptible to *T. gondii* infection. Illiteracy, living in rural areas, consuming raw vegetables**,** contact with soil, and high glucose levels are risk factors for diabetic patients. More studies are needed to explore the role of toxoplasmosis in developing diabetes 'complications.

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Informed Consent:
An informed written consent was obtained from each participant after explaining the purpose and procedures of this study.

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Conflict of Interest:
The authors declare no conflict of interest related to this study.

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