BMC Nephrology

RESEARCH

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Latent *Toxoplasma gondii* infection and associated risk factors among patients with chronic kidney disease: a registry-based study

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Abstract

Background Patients with chronic kidney disease (CKD) are susceptible to acquiring opportunistic parasites due to acquired immunodeficiency caused by uremia. Therefore, the present case–control study attempted to determine the prevalence of *T. gondii* infection and also associated risk factors among patients with CKD under hemodialysis and healthy controls who were registered at the Iranian National Registry Center for Toxoplasmosis (INRCT) in Mazandaran Province, northern Iran.

Methods 212 cases with CKD and 200 healthy controls were enrolled in this study. Informed consent as well as a questionnaire were obtained from all subjects. Blood samples were collected from each participant and the serum was screened for anti-*Toxoplasma* antibodies (IgG and IgM). PCR assay was performed to detect circulating *T. gondii* in the blood samples of patients and controls using the primer pair targeting the RE gene.

Results Out of 412 participants, 67.92% of patients and 15.5% of control subjects were positive for anti-*Toxoplasma* IgG, but all participants were negative for anti-*Toxoplasma* IgM. Also, considering PCR assays with RE target, the prevalence of *T. gondii* infection was 24.1% in case subjects, while none of the control subjects tested positive. Among the PCR positive, 34 (66.7%) had *Toxoplasma* IgG positivity. The results from the multiple multinomial logistic regression revealed that the seroprevalence of anti-*T. gondii* IgG antibodies in patients with CKD was 3.12 times higher than in healthy controls (OR = 3.12; 95% CI = 0.43, 14.8; $P < 0.001$). Also, there was a significant association between

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seroprevalence of *T. gondii* infection and age, having a cat at home, and level of glomerular filtration rate (GFR) in these patients.

Conclusion Our findings demonstrate a highly significant association between latent *T. gondii* infection and CKD, mostly in the late stages. Thus, regular screening for *T. gondii* infection in these patients is strongly recommended to prevent the reactivation of latent infections. A combination of serological screening, chemoprophylaxis, and PCR follow-up for patients at risk of reactivation should effectively reduce the likelihood of latent infection reactivation.

Clinical trial number Not applicable.

Keywords Chronic kidney disease, Glomerular filtration rate, Hemodialysis, Latent toxoplasmosis, *Toxoplasma gondii*

Introduction

Toxoplasmosis is a global zoonotic food-borne disease caused by the obligate, intracellular protozoan *Toxoplasma gondii* (*T. gondii*). It's one of the most successful intracellular parasite on the planet, which can infect all warm-blooded animals [1], and is one of the most common zoonotic diseases in the world [2]. Humans are infected with *T. gondii* by ingestion of undercooked meat containing tissue cysts, by intake of mature oocysts, and by maternal-neonatal transmission [3, 4]. The other ways of transmission are blood transfusions, solid organs allografts, or hematopoietic stem cell transplantation [5].

T. gondii can cause severe or life-threatening disease in pregnant women, individuals with immune deficiencies such as HIV/AIDS, individuals who have had organ transplants, and individuals undergoing chemotherapy [6]. The disease is usually covert or asymptomatic in individuals with healthy immune systems, and only a small percentage of them show mild symptoms, such as a mild fever, enlargement of lymph nodes, or muscle weakness [6]. Acute toxoplasmosis is commonly self-limiting in persons with a healthy immune system, while tachyzoites mostly transform to bradyzoites and remain inactive in a tissue cyst. Latent toxoplasmic cysts are usually detected in the tissues or the central nervous system and can serve as a reservoir for recrudescence when a person becomes immunocompromised [7].

Chronic Kidney Disease (CKD) is a condition characterized by a gradual decrease in the kidney's capability to filter blood, displaying itself as a permanent reduction in glomerular filtration rate (GFR) [8, 9].

CKD, in addition to imposing high costs on the health system, causes long-term physical and psychological complications in humans [10]. Approximately 500 million individuals are estimated to have CKD, with the majority (80%) of those individuals living in less developed countries [11]. The overall prevalence of CKD in different parts of the World is different. Thailand (17.5%) [12], South Africa (10.1%) [13]; African Sahara (13.2%) [14]; and USA (14.8%) [15]. Based on a recent meta-analysis and systematic review study, the overall prevalence of CKD is estimated 15.4% in Iran [16].

A very recent study reported that the levels of common CKD biomarkers were significantly higher among the *Toxoplasma*-positive participants [17]. Therefore, the present case–control study was attempted to assess the prevalence of latent *T. gondii* infection and the associated risk factors using serological and molecular techniques among patients with CKD under hemodialysis, compared to healthy controls who were registered at the Iranian National Registry Center for Toxoplasmosis (INRCT) at Mazandaran University of Medical Sciences (MAZUMS) in Sari, northern Iran.

Subjects and methods

Sampling

This case-control study was conducted on 212 patients aged between 30 and 90 years with CKD who were receiving regular hemodialysis, at Imam Khomeini Teaching Hospital in Sari, northern Iran. These patients comprised the case group. The control group consisted of 200 apparently healthy subjects registered at INRCT for routine screening of *T. gondii* infection, between January 2019 and December 2020. This study was reviewed and approved by the ethics committee of the MAZUMS, with an ethics number of IR. MAZUMS. REC.1398.6303. Informed consent was taken from all the contributors. Demographic data, including geneder, age, geographical location, food habits, also, much epidemiological information, was recorded and matched in the case and control groups. Also, patients with CKD were classified into 5 groups according to GFR. Inclusion criteria for selecting each participant in the control group included: no history of malignancy, leukemia, CKD and autoimmune disease, over 20 years.

ELISA assay

To determine the seroprevalence of toxoplasma infection, 5 mL of peripheral blood was taken from all participants. Blood samples were clotted at room temperature and then centrifuged at 500 ×g for 10 min, and the separated sera were stored at -20 °C in the laboratory of MAZUMS. In this study, anti-*toxoplasma* IgG and IgM were measured using the ELISA method with a commercial kit (PishtazTeb, Tehran, Iran) according to the

manufacturer's instructions. Accordingly, IgG absorbance levels < 9 were considered negative, 9–11 were considered borderline, and > 11 was positive; IgM absorbance levels < 0.9 were considered negative, 0.9–1.1 were assumed to be borderline, and > 1.1 was positive. All the results of the borderline tests were repeated two weeks later with the same kit.

Conventional PCR assay

We used the phenol-chloroform isoamidalcol method to extract *T. gondii* DNA from 412 buffy coat specimens. Conventional PCR (PCR) was done by forward primer F 5′-CGCTGCAGGGAGGAAGACGAAAGTTG-3′ and reverse primer R 5′-CGCTGCAGACACAGTGCATCT GGATT-3′, amplifying a 529 bp repeated element (RE) sequence [18]. The negative control in this method was sterile distilled water, whereas the positive control was DNA extracted from the tachyzoite strain RH.

Table 1 Association between *T. gondii* (positive/negative) status and CKD status [n (%)]

Variables	CKD Patients (%) (*n* = 212)	Healthy control (%) (*n* = 200)	*P*-value
Gender			
Male	103 (48.59)	101(50.5)	0.23
Female	109 (51.41)	99 (49.5)	
Age group			
30–40	13 (6.13)	10 (5)	0.03*
41–50	26 (12.27)	38 (19)	
51–60	49 (23.11)	41(20.5)	
61–70	74 (34.91)	80 (40)	
71–80	32 (15.09)	28 (14)	
> 80	18 (8.49)	3 (1.5)	
Serology test			
IgG positive	144 (67.92)	31 (15.5)	0.001*
IgG negative	68 (32.08)	169 (84.5)	
PCR assay			
PCR positive	51 (24.1)	0	0.001*
PCR negative	161 (75.9)	200	
Cat at home			
Yes	67 (31.60)	52 (26)	0.04*
No	145 (68.40)	148 (74)	
Uncooked meat consumption			
Yes	24 (11.32)	31 (15.5)	0. 25
No	188 (88.68)	169 (84.5)	
GFR			
Stage 1	4 (1.89)	0	0.01*
Stage 2	19 (8.96)	0	
Stage 3a	32 (15.09)	0	
Stage 3b	86 (40.57)	0	
Stage 4	71 (33.49)	0	

GFR: Glomerular filtration rate; *Significant at level of 0.05

Data analysis

The results of this study were determined using SPSS software Statistics, version 20.0 (IBM Corp., Armonk, NY, USA). We used a chi-square test to assess risk factors between case and control groups. Multivariate logistic regression analysis with 95% confidence was also used to calculate the adjusted (OR) odds ratio. In this study, we considered *P* values of less than 0.05 to be statistically significant.

Results

A total of 412 participants were examined, 212 had CKD (48.59% male and 51.41% female) and 200 were healthy controls (50.51% male and 49.5% female). Most of the participants were in the age group between 61 and 70 years. 40.57% and 33.49% of the patients with CKD were in stages 3b (an eGFR of 30 to 44 ml/min) and 4 (an eGFR of 15 to 29 ml/min), respectively.

The seroprevalence of anti- *T. gondii* IgG antibodies in the case and control groups was 67.92% and 15.5%, respectively. Also, anti-*Toxoplasma* IgM was not detected in any of the participants. Moreover, in PCR assays, *T. gondii* DNA was detected in 24.1% (51/212) of case subjects, while none of the control subjects tested positive. Among the 51 PCR positive, 34 (66.7%) had *Toxoplasma* IgG positivity. Moreover, 24 (47.1%) male and 27 (52.9%) female were PCR positive, but this difference was not statistically significant ($P = 0.14$).The highest proportion of *T. gondii* PCR positivity among CKD patients was observed in stage 4, with 35 out of 51 patients (68.62%) testing positive. This was followed by stage 3b, with 13 out of 51 patients (25.49%) and stage 3a, where 3 out of 51 patients (5.88%) were positive, The differences were statistically significant ($p = 0.041$). No PCR positivity was found in stages 1 and 2.

We found a statistically significant association regarding age, anti-*Toxoplasma* IgG test, PCR assay, and GFR variables between the two groups ($P < 0.05$). However, there were no differences in gender or uncooked meat consumption ($P > 0.05$). Table 1 shows the demographic characteristics of the case and control groups as well as the GFR in two groups.

The results from the multiple multinomial logistic regression revealed that the seroprevalence of anti-*T. gondii* IgG antibodies in patients with CKD was 3.12 times higher than in healthy individuals (OR = 3.12; 95% CI = 0.43, 14.8; $P < 0.001$). Also, age, having a cat at home, and level of GFR had a statistically significant association with *T. gondii* seropositivity in two groups ($P < 0.05$) (Table 2).

Table 2 Multiple logistic regression analysis for CKD status on *T. gondii* IgG antibody

Risk factor	Odds ratio (%95 CI)	*P* value
***T. gondii* seropositive**		
Cases	3.12 (0.43, 14.8)	0.001*
Controls		
Age group (years)	1.4 (0.11, 10.2)	0.03*
Cat at home	2. 24 (0.38, 12.14)	0.04*
GFR	2.8 (0.41, 11.02)	0.01*

*Significant at level of 0.05

Discussion

CKD is one of the fastest growing chronic diseases in the world today [19]. According to the evidence, patients undergoing hemodialysis are immunocompromised, owing to immune response dysfunction [20]. Thus, these patients are more susceptible than healthy individuals to acquiring opportunistic parasites, as a result dysfunction of their immune response [21, 22]. Therefore, the present study attempted to determine *T. gondii* infection in patients with CKD and healthy controls in Mazandaran Province, northern Iran. In a systematic review with a meta-analysis study, Foroutan et al. evaluated the pooled seroprevalence of latent and acute toxoplasmosis in patients undergoing hemodialysis up to December 2017 in Iran. They reported that anti-*Toxoplasma* IgG and IgM were detected among 58% and 2% of hemodialysis patients, respectively [21].

Based on our results, the anti-*T. gondii* IgG antibody was higher in patients undergoing hemodialysis than normal subjects (67.92% vs. 15.5%). In the previous survey, the seroprevalence rate of latent *T. gondii* infection in hemodialysis patients in Mazandaran was reported 80.0% [23]. The geographical climate is one of the key parameters of the *T. gondii* infection. Mazandaran Province in the northern part of Iran, with ideal mean humidity and annual rainfall, has a suitable condition for oocyst sporulation and survival in the environment. This conditions established a high prevalence of *T. gondii* infection in this part [23].

Our study similar to Babekir et al. results [17] confirms there is a significant relationship between toxoplasmosis and CKD. They showed that the positive *T. gondii* IgG subjects had significantly higher levels of albuminuria and estimated GFR stages compared to the negative subjects. Based on evidence, latent or covert *T. gondii* infection could injury kidney tissues [24]. However, the mechanism by which *T. gondii* exposure damages the renal system is still vague.

As *T. gondii* parasite has a complex life cycle, makes complex interactions with the host, and applies diverse immune responses in the human. The innate immune system is the primary reply to infection with the production of high levels of interleukin (IL)-12 and interferon (IFN-γ) [25, 26]. Also, in human cells, *T. gondii* persists by nitric oxide and reactive oxygen species producing, the secretion of chemokines and pro-inflammatory cytokines and cell decease induction [26]. The chronic effect of oxidative stress on kidney tissues is appointed by inflammation, following tissue damage, leading to probable organ dysfunction [27].

CKD develops in stages based on levels of kidney function. The kidneys are still capable of filtering out waste in the early stages, while this organ has lost most of its capabilities or stopped working in the latter stages [8]. In our study, the majority of PCR-positive patients with CKD were significantly categorized in stage 4 (68.62%). Based on the available literature, there is no evidence to suggest that specific stages of GFR may be associated with PCR positivity for *T. gondii* in patients with CKD or end-stage renal disease (ESRD). The literature generally points out that patients with impaired kidney function are at a greater risk for opportunistic infections like toxoplasmosis due to their compromised immune systems [17, 20, 21, 28]. Thus, it seems that this impairment can lead to higher rates of active infections detectable by PCR, especially in those with low GFR (stages 3and 4), where the body's ability to manage infections is significantly reduced. However, there is limited evidence to suggest that GFR stages associated with seropositivity of toxoplasmosis. A study focused on patients undergoing hemodialysis found that while seropositivity for *T. gondii* antibodies was high, PCR results indicated active infection in a small subset of these patients. Specifically, only 4 out of 280 blood samples from hemodialysis patients tested positive for *T. gondii* via PCR, suggesting that while the majority may have antibodies, the actual presence of the parasite (indicated by PCR) is less common but still significant in this population, particularly in advanced stages of CKD [28].

In summary, while direct studies correlating specific GFR stages with PCR positivity for *T. gondii* are limited, there is a trend suggesting that lower GFR levels (particularly stages 4) may be associated with higher rates of PCR positivity due to increased susceptibility to opportunistic infections in these populations. Further research is needed to establish definitive relationships and mechanisms underlying these observations.

Another study by Babekir et al. [17] indicated that the elevated levels of eGFR (stages 4 and 5) had higher proportions of seropositive subjects than negative subjects. Most of the patients with CKD in this survey were in stages 3b and 4 of the disease based on the level of GFR. This suggests that as kidney function declines, the risk of exposure or reactivation of latent infections may increase, potentially leading to higher serpositivity rates in these more advanced stages.

In addition to conventional serological assays, molecular assays are used for the diagnosis of *T. gondii* infection [29]. According to the data obtained in this survey, IgM antibodies were not detected in the patients and control groups. A serological technique is the primary method for the identification of *T. gondii*-specific antibodies, which indicate earlier exposure and or chronic (latent) infection. Thus, we selected PCR for detecting *T. gondii* positivity in peripheral blood due to its high sensitivity and specificity, which allows for rapid and accurate identification of acute /active infections. This is particularly important in our patient population, where timely diagnosis can significantly impact clinical management and outcomes. The ability of PCR to detect the presence of the parasite's DNA provides a definitive diagnosis, especially when serological results may be negative and ambiguous or delayed [30].

In our investigation, *T. gondii* DNA was detected in 24.1% of patients with CKD by PCR. These results were in accordance with the Mirahmadi et al. (2018), study, who reported the prevalence rates of anti-*T. gondii* IgM and *T. gondii* DNA in 0% and 29.4% of hemodialysis patients with chronic renal disease in Zahedan, southeastern Iran, respectively [31].

Surprisingly, out of 51 PCR positive cases for *T. gondii* DNA, 17 (33.3%) did not exhibit IgG *T. gondii* antibodies. Overall, the PCR assay evaluates circulating *T. gondii* DNA (cell-free DNA) or circulating tachyzoites in clinical samples, indicating active or acute infections. In contrast, serological methods detect antibodies, which indicate chronic (latent) infections. If the amount of antibodies produced is insufficient, the serological test may yield a negative result. Also, high levels of *T. gondii* specific IgG in some recently acquired toxoplasmosis patients may interfere with the IgM antibodies and cause false-negative results [32]. Furthermore, due to the dynamic nature of *T. gondii* tissue cysts, a positive *T. gondii* PCR result may not always indicate an acute stage of *T. gondii* infection. This is because *T. gondii* tissue cysts can undergo apoptosis, which may lead to a positive PCR result [33].

Based on multiple logistic regression results, there was a significant association between *T. gondii* IgG seropositivity and having a cat at home in both the case and control groups ($P<0.05$). Cats are the main animals that can excrete resistant oocysts, particularly in warm and moist areas, and they play an essential role in the epidemiology of *T. gondii* infection [34]. The awareness of CKD patients with this risk factor could lead to reduce exposure to the infective stages of this food-borne parasite. As a whole, the combination of increased susceptibility, risk of reactivation, impact on CKD progression, and availability of prophylactic interventions makes regular *Toxoplasma* screening an important part of comprehensive care for CKD patients.

Limitation

Although this study sought to determine the correlation between *Toxoplasma* infection and CKD, additional research is needed to clarify the nature of this relationship. A cohort study would offer deeper insights into how exposure to *Toxoplasma* affects outcomes over time. Additionally, a larger sample size would enable more detailed analysis of subsamples within the study, so caution is warranted when interpreting the results. Additionally, because our research was carried out at a single center, conducting studies across multiple centers would enhance the generalizability of the findings.

Conclusion

Our data show a highly significant correlation between covert or latent *T. gondii* infection and CKD, particularly in its late stages. Consequently, patients in the late stages pose a greater risk for *T. gondii* infection. Overall, regular screening of CKD patients for *T. gondii* infection is highly recommended to prevent the reactivation of latent infections. A combination of serological screening, chemoprophylaxis for patients at risk of reactivation, and PCR follow-up for high-risk individuals should effectively reduce the likelihood of latent infection reactivation. Early detection and management of *Toxoplasma* infection can significantly improve outcomes in this vulnerable population. Overall, the study highlights the importance of raising public awareness in the region to prevent the transmission of *T. gondii* infection and reduce the incidence of the disease.

Acknowledgements

We would like to appreciate the assistance offered by the colleagues at departments of Iranian National Registry Center for Lophomoniasis and Toxoplasmosis, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran.

Author contributions

M.M wrote the manuscript, collaborated in editing the final manuscript, reviewed and approved the final version that would be published. M.F, O.S and A.M contributed to the idea and design, data interpretation and reviewed the final draft that would be published. A.M contributed significantly to the idea and design, data interpretation and reviewed the final draft. R.T, M.N and M.S collected the samples, assisted with the data analyses. All authors have read and agreed to the published version of the manuscript.

Funding

The study was funded by Mazandaran University of Medical Science, Project No IR.MAZUMS.REC.1398.6303. No external funding was received.

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This study was ethically approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1398.6303), and all procedures adhered to ethical rules and principles set forth in the Declaration of Helsinki. Also, Informed consent was obtained from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 26 November 2024 / Accepted: 18 March 2025
Published online: 31 March 2025

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