

## Review Article

### A REVIEW ON THE EFFECT OF TOXOPLASMOSIS ON HUMAN BEING

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#### ABSTRACT

*Toxoplasma gondii* is an obligate intracellular protozoan parasite that infects all warm-blooded animals including humans. *T. gondii* infection cause development of central nervous system disorders, which may lead to altered behaviour in the affected individuals. The ingestion of raw and semi-cooked meat containing viable cysts has been suggested to be one of the major sources of infection. In the present investigation, the databases of PubMed, Google Scholar and Iran Doc were examined from 2000 to 2021 and related articles were reviewed. Review of related investigations revealed that *T. gondii* infection has been observed to play the greatest role in suicides, and psychiatric patients. It showed that *T. gondii* infection associate with schizophrenia, bipolar disorder, depressive disorder, addiction and obsessive-compulsive disorder. Besides, in severe cases the parasite may cross the placenta of an infected pregnant woman and probably infect the fetus congenitally. The current investigation is especially useful for health organization, pet owners, women and particularly pregnant women. Thus, consideration of the clinical factors, and laboratory results are important for diagnosis. Now more than ever, new strategies are desired to control *T. gondii* transmission.

**Keywords:** *Toxoplasma gondii*, Toxoplasmosis, Infection, Human being.

#### INTRODUCTION

*T. gondii* is a common parasite around the world and it is capable of adapting many species of intermediate hosts. Besides, it is one of the most common reasons of an thropozoonosis. The occurrence of *T. gondii* infection among human being differs extensively based on the sanitary conditions, climate zone, and nutrition (Flegr, Prandota, Sovickova & Israili, 2014). For several years, the latent phase of toxoplasmosis was found to be totally asymptomatic in immunocompetent persons. The contagion was considered helpful due to the attained immunity protecting women in contradiction of severe infection during pregnancy and the contagion of the fetus. Latent *T. gondii* infection among people was supposed to trigger a number of anomalies, result in lack of attentiveness, poorer reactions, and abridged feeling of fear (Flegr, 2007; Flegr, 2013). Furthermore, the assessed seropositive women confirmed augmented levels of violence, and men's extreme rashness (Cook *et al.*, 2015). These characters are serious and may pose a health risk. The traits leading to possibly harmful behavior disorders are supposed to be result of cerebral changes in *T. gondii* infected people. One of fluctuations is deregulation of cerebral neurotransmitters, particularly deregulation of dopamine (Prandovszky, *et al.*, 2011; McConkey, Martin, Bristow & Webster, 2013). Likewise, recent study showed that drinking milk was a risk factor for toxoplasmosis (Boughattas, 2017) and some studies associated raw goat's milk consumption with human contagions (Dubey, 2010). Toxoplasmosis is a parasitic zoonosis for human being (Boughattas, *et al.*, 2014). Seroprevalence of *Toxoplasma* contagion among immunocompromised patients is high and recrudescence of latent contagions among them can be dangerous (Zhou, *et al.*, 2011). Moreover, through chronic toxoplasmosis, both CD4+ and CD8+T lymphocytes are essential to stop recrudescence of toxoplasmosis. Therefore, reduction of T cells in the setting of chronic contagion as in depressed cellular immunity statuses, lead to

recurrence of latent contagion (Amichay, *et al.*, 1996). Cirrhosis is thought as an immunocompromised phase that result in diversity of infections, which account for estimated 30% mortality rate (Tandon & Garcia-Tsao, 2008). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses which affect nearly 600 million people around the worldwide. In this regard, liver cirrhosis and hepatocellular carcinoma are due to chronic contagions which cause 1 million deaths every year (Schmidt, Blum & Thimme, 2013). *Toxoplasma* and hepatitis viruses are intracellular pathogens which inspire immune responses including Th1 cytokine profiles and IL-12, IFN- $\gamma$  and nitric oxide (Jankovic, Liu & Gause, 2001). Co-infection by more than one pathogen is prevalent in developing countries. Besides, it affects the host immune response by persuading changes in host physiology (Supali *et al.*, 2010). *T. gondii* is an intracellular protozoan parasite that affect all warm-blooded animals including human being (Dubey, 2010). The life cycle of *T. gondii* comprises felines as the absolute host and mammals and birds as communal intermediate hosts. Oocysts formed in the host are expelled in faeces, before being ingested by an intermediate or another host. After digestion, sporozoites are ejected from the oocyst, emerging into tachyzoites and chiefly trigger muscles or neural tissues where the parasite grows into a tissue cyst, the site of bradyzoite duplication. The number of bradyzoites in tissue cyst depends on the age and size of the cyst (Dubey, 1998). Excluding instances of inherited or sexual transmission, blood transfusion or organ transplantation, it's not passed from person to person (Guerina *et al.*, 1994). The point is that digestion of raw or rare meat encompassing viable cysts has been optional to be the major bases of contagion in Europe and North America. In this regard, *T. gondii* was ranked in fourth place in a multi criteria-based risk ranking of food borne parasites compiled by the Food and Agriculture Organization (FAO)/World Health Organization (WHO) in 2014 (WHO/FAO, 2014). In addition, *T. gondii* contagion led UK Food Standards Agency (FSA) and the European Food Safety Authority (EFSA) to carry out meetings and share scientists' ideas on main features of the parasite-host collaboration (FSA, 2012; Opsteegh *et al.*, 2016).

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Though different studies recognized meat products as a significant source of *T. gondii* contagions among human being, numerical sympathetic of the risk imposed to humans via food chain is astonishingly limited. Whereas probabilistic risk evaluation for some pathogens such as *Campylobacter jejuni*, *Listeria monocytogenes* or *Escherichia coli* have been recognized, efforts to measure the likelihood of human exposure to *T. gondii* via eating products of animal are at early phases. In this regard, Crotta, Limon, Blake & Guitian (2016) directed a study on the assessment of human being contact to *T. gondii* via meat products. The findings showed that the input parameters had the highest effect on the output mean. Recent investigations (e.g., Deng *et al.*, 2016; Opsteegh *et al.*, 2016) have begun to complete some of knowledge gaps in this realm. Recent investigations in this realm can offer evidence on the association without comes of serological tests and occurrence of the parasite in different species' meat, predilection tissues and the regularity of contact in livestock animals.

## REVIEW OF LITERATURE

*T. gondii* infects one-third of the entire population frequently around the world and in an immunocompromised patient or an infected fetus, it may result in overwhelming effects. The parasite may pass the placenta of an infested pregnant woman and possibly infect the fetus. In this regard, congenital toxoplasmosis may cause hepatosplenomegaly, abortion, jaundice, intra-uterine growing restriction or death. It may lead to hydrocephalus or retinochoroiditis and neurological or intracranial calcifications. It worth mentioning that severe toxoplasmosis in immunodeficient patients who do not have AIDS showed neurological challenges. These challenges comprised headache, seizures, focal neurologic deficit, cranial nerve deficit, meningoencephalitis, encephalitis and disequilibrium (Khan & Khan, 2018). Furthermore, inherited toxoplasmosis may occur with severe results such as fetal loss, death in utero, intra uterine growth delay, encephalitis, hydrocephalus, psychological illness, aural and

Premature infants infected with *T. gondii* may suffer from ocular illness in the first three months of life. It worth mentioning that if the inflammatory illnesses, cardiovascular abnormalities, ocular injury such as retinochoroiditis (Oz & Tobin, 2012; Wallon, *et al.*, 2014). diseased infant is full-term, the illness is typically milder with hepatosplenomegaly and lymphadenopathy in the first two months of lifetime (Jones, Lopez & Wilson, 2003). In addition, clinically recognized disease in newborns, will lead to jaundice, eosinophilia, abnormal cerebrospinal fluid, cerebral calcifications, lymphadenopathy and enlargement of the spleen or liver. Here, Neurological symptoms might include bulging fontanelle, nystagmus, micro or macrocephaly, seizures and abnormal muscle tone (Steele, 2007). The other point concerning *T. gondii* refers to different epidemiological investigations outcomes about asthma. Some findings showed opposite association between asthma occurrence and chronic contagions such as *Helicobacter pylori* (Blaser *et al.*, 2008), hepatitis A and *T. gondii* (Ellertsen *et al.*, 2008; Fernandes *et al.*, 2010). On the other hand, some studies showed that not only chronic infections such as *T. gondii* or *Helicobacter pylori* (Fenoy *et al.*, 2009; Arnold *et al.*, 2011), but also infection via viruses, bacterium and helminthes modulate immune responses (Wohlleben *et al.*, 2003; Kitagaki K *et al.*, 2006). It worth mentioning that *T. gondii* also resulted in mental disorders (Sutterland *et al.*, 2015). Newly meta-analysis investigated *T. gondii*'s effect on schizophrenia, psychological disorder and bipolar challenges. The results show edits significant effect on schizophrenia, addiction and bipolar disorder (Sutterland *et al.*, 2015). Equally, some studies revealed association between *T. gondii* and anxiety symptoms (Groër *et al.*, 2011; Duffy *et al.*, 2015), anxiety disorder (Markovitz *et al.*, 2015), obsessive-compulsive complaint (Miman *et al.*, 2010), suicide (Zhang *et al.*, 2012), mixed anxiety and depressive disorder (Alvarado-Esquivel *et al.*, 2016) and aggression and impulsivity (Cook *et al.*, 2015). Though, negative outcomes are available in this regard (Gale *et al.*, 2014; Sugden *et al.*, 2016). Following table highlights the evolution of studies in this realm.

**Table 1. Evolution of toxoplasmosis studies around the world**

Name of researchers	Name of study	Year of study	Main findings
Peyron, Wallon, Liou & Garner	Treatments for toxoplasmosis in pregnancy	2000	Result revealed that treating the diseased mothers with spiramycin during pregnancy abridged the transmission rate to the fetus from 56% to 24%.
Bosche <i>et al.</i> ,	Ocular toxoplasmosis: clinical features and prognosis of 154 patients.	2002	The efficiency of treatment with pyrimethamine and azithromycin was similar to the standard treatment with pyrimethamine and sulfadiazine.
Roque-Resendiz, Rosales & Herion Az sheshom	MVA ROP2 vaccinia virus recombinant as a vaccine candidate for toxoplasmosis	2004	The findings showed that ROP2 could persuade the generation of protecting antibodies, IgG1 and IgG2, against Toxoplasmacontagion.
Fernandesa <i>et al.</i> ,	Antibody and cytokine responses to house dust mite allergens and <i>T. gondii</i> antigens in atopic and non-a topic Brazilian subjects.	2010	<i>T. gondii</i> contagion could block the growth of allergic airway irritation.
Kornacka <i>et al.</i> ,	The usefulness of direct agglutination test, enzyme-linked immunosorbent assay and polymerase chain reaction for the detection of <i>T. gondii</i> in wild animals	2016	Enzyme relatedto immunosorbent assay and agglutination test are appropriate for <i>T. gondii</i> antibody discovery in meat juice from wild animals. Positive outcomes by immunological tests do not show that the host was infected by <i>T. gondii</i> . PCR should be used to confirm the result.
Ozgonul & Besirli	Recent developments in the diagnosis and treatment of ocular toxoplasmosis	2017	Oral administration of a mixture of pyrimethamine and azithromycin presented better outcomes against ocular toxoplasmosis.
Suvisaari <i>et al.</i> ,	Toxoplasma gondii infection and common mental disorders in the Finnish general population	2017	<i>T. gondii</i> seropositivity is allied with anxiety disorder, depressive symptoms and comorbid depressive and anxiety disorders.

Table 2. Evolution of toxoplasmosis studies in Iran.

Name of researchers	Name of study	Year of study	Main findings
Saadatnia & Golkar	A review on human toxoplasmosis	2012	The occurrence of <i>T. gondii</i> seropositivity was diverse noticeably by region, age, and ethnic group.
Shomakhte, Javadnoori, Jefride & Saki	Investigating the relationship between premature rupture of fetal membranes and infection <i>T. gondii</i> in pregnant women with preterm labor	2016	The impact of <i>Toxoplasma</i> on preterm delivery, was due to mechanisms other than premature rupture of membranes.
Majidiania, Dalvand, Daryani, Ramirezd & Foroutanrad	Is chronic toxoplasmosis a risk factor for diabetes mellitus? A systematic review and meta-analysis of case-control studies	2016	Meta-analysis highlighted chronic toxoplasmosis as a probable risk factor for type 2 DM. According to random effects model no statistically significant association was experienced between <i>T. gondii</i> and type 1 DM.
Mahmoudi, Mamishi, Suo & Keshavarz	Early detection of <i>T. gondii</i> infection by using a interferon gamma release assay: A review	2017	The findings highlighted the importance of assessing cellular immunity to establish an early diagnosis for inherited toxoplasmosis. ELISA-based Interferon-gamma release assay (IGRA) was a beneficial diagnostic tool for early recognition.
Faridnia, Daryani, Sarvi, Sharif & Kalani	Vaccination against <i>Toxoplasma gondii</i> using rhoptry Antigens	2018	The ROP2 was the most frequently used ROPs in DNA vaccines (27.27%) and protein vaccines (6.81%).
Ahmadi, Zarifi, Shokrani & Noruzian	Serum prevalence and molecular study of <i>Toxoplasma</i> infection in native chickens of Khorramabad city, Iran	2020	The findings designated the significant role of native chickens as a source of infection for cats and people living in rural areas.

### Treatment and Diagnosis

Felids are the final hosts for the parasite where it undergoes sexual replication in their gut. Ecologically resilient oocysts are released in the feline feces. The oocysts become transmittable when they undergo sporulation in the soil in satisfactory circumstances (Yolken, Torrey & Dickerson, 2017). When it inadvertently swallowed by mammals, grows into tachyzoites. Then, it spreads in blood to contaminate all tissues chiefly the CNS, eyes, muscles, and placenta (Many & Koren, 2006). Here, Tachyzoite contaminates nucleated host cells and uses the dendritic cells, macrophages, and monocytes. Then, it attacks the host immune system and evades the blood-brain barrier and the placenta barricade. Finally, it spreads and form systemic disease (Elsheikha & Khan, 2010). In countries like Austria, France and Germany serologic screening programs have been developed to examine the transfer of the contagion to the fetus (Cortina-Borja, *et al.*, 2010). Several methods for the analysis of toxoplasmosis are suggested in this regard. They can be considered as direct and indirect approaches. In this case, *T. gondii* DNA can be detected from body liquids via PCR, cell culture, ophthalmic test, radiological investigations and demonstration of the parasite through mouse immunization, which are considered as direct diagnosis approaches, whereas indirect diagnosis approaches include recognition of anti-*Toxoplasma* antibodies via ELISA and Sabin-Feldman dye test (Kwofie, *et al.*, 2016). In addition, *Toxoplasma* specific immunoglobulin's (IgG and IgM) tests are regularly applied to determine whether a pregnant woman has attained the infection. It worth mentioning that the treatment routines comprise spiramycin to stop congenital transmission from an infected mother. Moreover, sulfadoxine, pyrimethamine and folic acid are practical to cure the infected fetus, CSF shunting for hydrocephalus. Besides, a combination of pyrimethamine, azithromycin, and corticosteroids for treating ocular toxoplasmosis are recommended ones in this dominion.

### Recent and future developments

Forthcoming developments of the molecular base of *Toxoplasma* pathogen city might be smoothed by newly advanced selective whole-genome sequencing (WGS) skills established with the thoroughly associated plasmodium malariae parasite. This method permits WGS straightly from clinical samples and, if effectively applied to *Toxoplasma*, it would allow sequencing of a greater number of parasite strains without the need for separation and culture, which is problematic and difficult. Here, culture may also not be conceivable for other explanation, for example due to non-viability of the organism in samples that have been kept and transported to the test center (Hadfield & Guy, 2017).

### CONCLUSION

The review revealed that *T. gondii* can infect all mammalian and recently infected nearly 1e2 billions of human being around the world. *Toxoplasma* oocysts in cat faeces can pollute the environment. Communal infection directions for human being are digestion of oocysts directly from the environment or via raw unwashed vegetables and fruit, or it may occur due to eating of viable tissue cysts in undercooked meat. Besides, *Toxoplasma* infection in immunocompetent persons is commonly asymptomatic but appears as a mild to moderate flu or glandular fever-like disease in 10e20% of patients (Hadfield & Guy, 2017). It worth noting that freezing meat before cooking is a simple way to decrease risk of food borne infection. In case of diagnosis, cerebrospinal fluid and amniotic fluid directed for recognition of *Toxoplasma* by nucleic acid amplification testing should not be assumed prior centrifugation for other surveys, because, this possibly removes the parasites from suspension. In this regard a clear low-level immunoglobulin G (IgG) seroconversion is observed in a formerly seronegative individual who has been given blood products, the possibility for passive gaining of IgG from the

contributors should be considered. The findings of this review are beneficial for health organization, women especially pregnant women and pet owners. It worth noting people about their consumption habits of eating raw or semi-cooked meat and unwashed vegetables and fruit. Additionally, pet owners should consider that exposure with cat faeces is a transmission rout of this parasite.

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