Toxoplasmosis seroprevalence in rheumatoid arthritis patients: A systematic review and meta-analysis

Zahra Hosseininejad1,2,3, Mehdi Sharif1,2, Shahabeddin Sarvi1,2, Afsaneh Amouei1,2, Seyed Abdollah Hosseini1,2, Tooran Nayeri Chegeni1,2, Davood Anvari1,2, Reza Saberi1,2, Shaban Gohardehi1, Azadeh Mizani1, Mitra Sadeghi2, Ahmad Daryani1,2*

1 Toxoplasmosis Research Center, Mazandaran University of Medical Sciences, Sari, Iran, 2 Department of Parasitology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran, 3 Student Research Committee, Mazandaran University of Medical Sciences, Sari, Mazandaran, Iran

* daryani@yahoo.com

Abstract

Background

Toxoplasmosis is a cosmopolitan infection caused by an intracellular obligatory protozoan, Toxoplasma gondii. Infection to this parasite in immunocompetent patients is usually asymptomatic, but today it is believed that the infection can be a risk factor for a variety of diseases, including rheumatoid arthritis (RA). RA is an autoimmune disease and the most common type of inflammatory arthritis that is a major cause of disability. The aim of this systematic review and meta-analysis was to address the association between RA and toxoplasmosis in light of the available research.

Methods

Based on the keywords, a systematic search of eight databases was conducted to retrieve the relevant English-language articles. Then, the studies were screened based on the inclusion and exclusion criteria. The random effect model was used to calculate the odds ratio (OR) using forest plot with 95% confidence interval (CI).

Results

Overall, 4168 Individual, extracted from 9 articles were included for systematic review evaluation, with 1369 RA patients (46% positive toxoplasmosis) and 2799 individuals as controls (21% positive toxoplasmosis). Then, eight articles (10 datasets) were used for meta-analysis (1244 rheumatoid arthritis patients and 2799 controls). By random effect model, the combined OR was 3.30 (95% CI: 2.05 to 5.30) with P < 0.0001.

Conclusion

Although toxoplasmosis could be considered as a potential risk factor for rheumatoid arthritis, more and better quality studies are needed to determine the effect of T. gondii infection.
on induction or exacerbation of RA. Our study was registered at the International Prospective Register of Systematic Reviews (PROSPERO; code: CRD42017069384).

Author summary

Toxoplasma gondii is an intracellular obligatory protozoan, which causes toxoplasmosis. T. gondii infection in immunocompetent individuals is mostly asymptomatic, but it may be reactivated as a result of immune disorders inducing serious complications. Rheumatoid arthritis (RA), as a complex autoimmune disease, is a major cause of significant and progressive disability, articular complications, and premature death. Studies confirmed an interaction between infections and environmental factors as the potential risk or protective factors determining the development of autoimmune diseases. In this study, we investigated the association between toxoplasmosis and RA.

Introduction

Toxoplasmosis is a parasitic disease with worldwide distribution caused by obligate intracellular coccidian protozoan Toxoplasma gondii (T. gondii) [1]. It is estimated that one-third of the world’s population are infected with this parasite in both developed and developing countries [2, 3]. Humans can be infected with the parasite through different routes, including consumption of raw or undercooked meat containing tissue cysts of the parasite, ingestion of sporulated oocysts from contaminated water and food, and vertical transmission during pregnancy through the placenta to the fetus [4].

T. gondii remains in the infected host tissues perpetually [5]. Most immunocompetent individuals, if infected with this parasite, are asymptomatic or show minor symptoms [6]. The most common symptom of toxoplasmosis in humans is lymphadenopathy that may be associated with fever, sore throat, muscle pain, fatigue, and headache [4]. In congenitally infected and immunocompromised patients, this disease is more likely to bring about severe complications [7]. Myocarditis and polymyositis have been reported in immunocompetent individuals with acute toxoplasmosis [8]. Furthermore, toxoplasmosis may cause polyarthritis in the hand and knee joints [9]. Polytenosynovitis (inflammation of a tendon sheath) caused by T. gondii has also been reported [10].

Rheumatoid arthritis (RA) is a common autoimmune disease, which is a major cause of inflammation of the joints and the principal cause of disability that affects 0.5–1% of the population [11, 12]. The disease presents with swollen joints, production of autoantibodies (rheumatoid factor), and systemic effects [13].

In recent years, the role of infectious agents, especially bacteria and viruses, has been identified in the pathogenesis of autoimmune diseases, while the role of parasitic infections due to their vague effects on host immunity has not been well-investigated. Experimental evidence may support the protective effect of specific parasitic infections in the susceptibility to autoimmunity [14]. Some geoepidemiological studies showed that host genetic susceptibility interacts with lifestyle and environmental factors, such as socioeconomic status, dietary habits, environmental pollutants, and ultraviolet radiation exposure; further, infections increase the risk of developing autoimmunity [15]. On the other hand, infectious diseases may contribute to the development of autoimmune diseases through molecular mimicry and epitope spreading [16].
Therefore, the aim of this systematic review and meta-analysis was to provide an updated review of data about the relationship between toxoplasmosis and RA.

**Methods**

**Search strategy**

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and its checklist [17]. Individuals with RA, along with a control group, were surveyed. To begin, we searched scientific databases for all the articles on the association between toxoplasmosis and RA published up to the first of January 2018. These keywords were used alone or in combination: "Toxoplasma gondii", "toxoplasmosis", "sero-prevalence", "prevalence", "rheumatoid arthritis", "rheumatoid factor", "meta-analysis", and "systematic review".

A literature review was carried out using English databases including "PubMed", "Google Scholar", "Science Direct", "Scopus", "Web of Science", "EMBASE", "CINAHL", and "Pro-Quest". The systematic search of articles was conducted from March 4 to December 31, 2017 by two researchers independently. Also, for completing the checklist, we investigated all the references lists of the selected articles manually. In this study, only English-language articles were analyzed; furthermore, unpublished studies were not evaluated.

**Study selection**

After completing the search, the selected articles were reviewed by the two researchers independently. All the duplicate and irrelevant studies were excluded after reviewing the title, abstract, and full text of the articles. Moreover, to prevent reprint bias, the results of the articles were carefully investigated and duplicates were omitted.

**Quality assessment**

In order to assess the quality of reporting of the studies, standard Strengthening the Reporting of Observational Studies in Epidemiology checklist (STROBE) was used [18]. S1 Checklist represents the quality score of different eligible studies. This checklist included items assessing the study methodology, study type, study population, sample size, sample collection methods, statistical tests, and presentations. In our study, articles were evaluated based on STROBE assessment (low quality: less than 16.5, moderate quality: 16.6–25.5, and high quality: 25.6–34). The articles we entered in our meta-analysis had acceptable quality.

**Inclusion and exclusion criteria**

Abstracts and full texts were assessed independently by the two researchers using a piloted form. The final decisions about the eligibility or exclusion of studies were made separately. Disagreements were resolved with provision for arbitration from a third reviewer. Following the removal of duplicate entries, articles were evaluated according to the following criteria: (1) cohort or case-control studies about the relationship between toxoplasmosis as an exposure and rheumatoid arthritis as a disease, (2) the studies conducted only on humans, (3) the presence of case and control groups, (4) the studies where toxoplasmosis was diagnosed by detecting IgG and/or IgM antibodies against T. gondii in individuals with definitive diagnosis of RA, and (5) the studies providing details on the seroprevalence rate of toxoplasmosis and RA.

The exclusion criteria comprised: (1) studies that were only descriptive, (2) studies that only presented the final result and did not provide the raw data, (3) articles that were not available in English language, and (4) the studies conducted on animals.
Data extraction

Articles were carefully studied and the following data were extracted: first author, year of publication, the number of patients and controls, the number and percentage of the positive and negative samples, and any other relevant data.

Records that were seen in the preliminary searches on databases (n=8234)

Records that were selected after a primary screening (n=124)

Records after duplicates removed (n=59)

Excluded articles by title and abstracts screening (n=43)

Articles screened by full-text (n=16)

Included article after References checking (n=3)

Full text articles assessed for eligibility (n=19)

Excluded criteria:
- Descriptive studies
- Studies in animal models
- None-English databases
- Studies without raw data (number of controls or cases and positive or negative) (n=10)

Studies included in qualitative synthesis (systematic review) (n=9)

Studies included in quantitative synthesis (meta-analysis) (n=8): Two studies had 2 datasets

Fig 1. Flow diagram of the study design process.

https://doi.org/10.1371/journal.pntd.0006545.g001
negative cases of serum IgG and IgM in patients and controls, as well as information about age and gender and laboratory results. In studies where two different populations were studied, data were extracted separately.

**Statistical analysis**

The meta-analysis was executed with the Stats Direct statistical software (http://statsdirect.com). For displaying the heterogeneity between studies, $\chi^2$-based Cochrane test (Q) and $I^2$ index were applied [19]. Due to significant heterogeneity between the studies, a random effect model was used to combine the results of the studies. Forest plot was used to indicate the prevalence of toxoplasmosis in each study and to determine pooled estimate prevalence in the studies. Odds ratios (ORs) and 95% confidence intervals (CI) were used for estimating the risk of *T. gondii* infection (the significance of $P<0.05$). OR $>1$ indicates the positive effect of *Toxoplasma* on RA and an OR $<1$ shows that toxoplasmosis has a protective effect against RA. Publication bias was examined by funnel plots and the statistical significance was assessed by the Egger test [20]. Also, it was performed a sensitivity analysis to identify probably effect of each article on the overall results by excluding them using Stata version 14 (Stata Corp, College Station, TX, USA).

The study protocol (CRD42017069384) was registered on the website of the International Prospective Register of Systematic Reviews (PROSPERO) [21].

**Results**

Our preliminary search of eight databases yielded 8234 papers. After a primary screening of the titles of the articles based on keywords, 124 studies were extracted. Sixty-five articles were

### Table 1. Baseline characteristics of the included studies in the systematic review and meta-analysis of the relationship between *T. gondii* infection and RA patients.

| No | First author | Publication year | Place of study | Type of study | Method | Test | Results | Age | Sex |
|----|--------------|-----------------|----------------|---------------|--------|------|---------|-----|-----|
| 1  | Shapira Y [14] | 2012 | Europe | Case control | BioPlex 2200 system | IgG | Significant | - - | - - |
| 2  | Shapira Y [14] | 2012 | Latin America | Case control | BioPlex 2200 system | IgG | Not significant | - - | - - |
| 3  | Fischer S [16] | 2013 | Europe | Cross sectional | Chemiluminescence | IgG | Significant | P: 40–74 C: - - | - - |
| 4  | Kuba RH [27] | 2014 | Iraq (Treated patients) | Case control | ELISA | IgG | Significant | P: 20–80 C: - - | - - |
| 5  | Kuba RH [27] | 2014 | Iraq (Untreated patients) | Case control | ELISA | IgG | Significant | 20–80 C: - - | - - |
| 6  | Al kalaby RF [22] | 2016 | Iraq | Case control | ELISA | IgG | Significant | P: 16–50 C: 16–50 | F |
| 7  | El-Sayed NM [25] | 2016 | Egypt | Case control | EIA | IgG | Significant | P: 30–58 C: 29–57 | P: (F:70, M:30) C: (F:34, M:16) |
| 8  | Flegr J [26] | 2016 | Czech and Slovak cohort | ELISA | CFT | IgG | Significant | - - | P: (F:10, M:3) C: (F:935, M:372) |
| 9  | El- Henawy AA [24] | 2017 | Egypt | Cross sectional | ELISA | IgG | Significant | P: <60 C: <60 | P: (F:29, M:31) C: (F:28, M:32) |
| 10 | Tian A-I [28] | 2017 | China | Case control | ELISA | IgG | Significant | - - | P: (—) C: (F:454, M:366) |
| 11 | Al- Oqaily MA [23] | 2017 | Iraq | Case control | ELISA | IgG | Significant | P: 13–68 C: 13–68 | - - |

Age is in years, ELISA: enzyme-linked immunosorbent assay, EIA: enzyme immunoassay, CFT: complement fixation test, IgG: Immunoglobulin G, IgM: Immunoglobulin M, P: Patient, C: Control, F: Female, M: Male

[https://doi.org/10.1371/journal.pntd.0006545.t001](https://doi.org/10.1371/journal.pntd.0006545.t001)
also excluded from the study due to duplication. In the next step, by screening the abstracts of the articles and based on the inclusion/exclusion criteria, 43 other articles were excluded. After reading the full text of the articles, 10 other papers were omitted, and three studies were added to the collection after reviewing the references. After the final review of the articles, nine eligible studies [14, 16, 22–28] were identified for systematic review. Another study was excluded due to the absence of a healthy control group [16]. Finally, eight of these nine articles [14, 22–28] were entered into the meta-analysis with respect to the inclusion/exclusion criteria (Fig 1).

The studied articles were published between 2007 and 2017. We identified 11 datasets from the nine articles that met the inclusion criteria, eight of which were case-control, two cross-sectional, and one were cohort studies (Table 1). The surveys were conducted in Latin America [14], Europe [14, 16], Egypt [24, 25], Iraq [22, 23, 27], Czech and Slovak [26], and China [28].

Our meta-analysis was performed among 4168 people including 1369 RA patients and 2799 controls. In all the studies, blood samples were collected from patients and controls. To identify anti-Toxoplasma antibodies (IgG and IgM) in those studies, ELISA [22–24, 26–28], CFT [26], EIA [25], chemiluminescence [16], and BioPlex 2200 system [14] were used (Table 1).

Except for Fischer et al. [16], who only evaluated IgG, other authors surveyed both IgG and IgM antibodies. However, only three studies had reported a titer of antibodies [23–25], and

![Proportion meta-analysis plot](https://doi.org/10.1371/journal.pntd.0006545.g002)

**Fig 2. Forest plot of seroprevalence rates of toxoplasmosis in rheumatoid arthritis patients.** *Patients under treatment.*

https://doi.org/10.1371/journal.pntd.0006545.g002
others had described the percentage of positive antibodies in patients and controls. Finally, all the studies analyzed the relationship between toxoplasmosis and RA with respect to the percentage of seropositive and seronegative individuals (patients and controls).

As shown in Fig 2, the prevalence of toxoplasmosis in RA patients in these studies varied from 25% to 77% with an overall seroprevalence of 46% (95% CI [37; 56]). However, the total prevalence of this disease in the control subjects entered in these studies was 21% (95% CI [14; 28]), which varied from 0% to 48% in various studies (Fig 3).

According to Fig 4, the odds of toxoplasmosis in RA patients are 3.30 times compared to that of controls with 95% CI: 2.05 to 5.30 and $P < 0.0001$. Nonetheless, the heterogeneity analysis of the effect size of arthritis ($Q = 32.77$, $P = 0.0001$, $I^2 = 72.5\%$) showed a relatively high heterogeneity in our meta-analysis.

Begg and Egger tests were used to evaluate publication bias. Negligible publication bias was observed using both Begg test ($P = 0.0286$) and Egger test ($P = 0.0446$) in the included studies. The results of sensitivity analysis showed that the impact of each study on meta-analysis was not significant on overall estimates (Fig 5).

**Discussion**

*Toxoplasma gondii* is an important opportunistic parasite infecting one-third of the world’s human population and it is considered a silent threat [29]. Though a clear relationship

![Proportion meta-analysis plot](https://doi.org/10.1371/journal.pntd.0006545.g003)

*Fig 3. Forest plot of seroprevalence rates of toxoplasmosis in controls groups.* *\* Patients under treatment.
between toxoplasmosis and autoimmune diseases, including RA, has not yet been well documented, a higher prevalence of anti-\textit{T. gondii} antibodies was reported in patients with rheumatoid arthritis [16]. Thus, we designed this systematic review and meta-analysis to explore the possible association between \textit{Toxoplasma} infection and RA, an autoimmune disease causing pain and disability [30].

Although few studies were included in our meta-analysis, our findings showed that the prevalence of toxoplasmosis in the control group was 21%, which is almost in agreement with the results obtained by Dubey and Beattie [31]. This seroprevalence was significantly different from the prevalence in RA patients (46%).

According to Table 2, the lowest OR was reported in Latin America and the highest OR in Europe. The difference in ORs can be attributed to the significant difference in host response and virulence of parasitic strains [32]. In addition, we found high heterogeneity in the relationship between RA and \textit{T. gondii} infection in this systematic review. The high heterogeneity index is suggestive of potential variation, which could be due to difference in genetic potential of humans, which is affected by lifestyle and environmental factors such as dietary habits, environmental pollution, exposure to ultraviolet radiation, various types of infections, and socio-economic status [33].

Our findings suggest that \textit{T. gondii} may trigger a pathologic process in individuals, which can ultimately lead to RA. This finding has been reported in other autoimmune diseases such as diabetes mellitus [34, 35], lupus erythematosus [36], and autoimmune thyroid diseases [37]. The higher prevalence of \textit{T. gondii} in people with chronic diseases can be explained by the following reasons: 1) toxoplasmosis can contribute to the progression of chronic diseases and 2)
Table 2. Data extracted from the included studies in the meta-analysis for an association between toxoplasmosis and RA.

| No | Reference                | N   | Case: RA+ (n) | Control: RA- (n) | RA+ & T+ (n, %) | RA- & T+ (n, %) | OR (95% CI) | P-value |
|----|--------------------------|-----|---------------|------------------|-----------------|-----------------|-------------|---------|
| 1  | Shapira Y [14] (Latin America) | 292 | 152           | 140              | 55 (36.18%)     | 50 (35.71%)     | 1.02 (0.62–1.70) | NS |
| 2  | Shapira Y [14] (Europe)    | 332 | 35            | 297              | 27 (77.14%)     | 77 (25.93%)     | 9.64 (4.02–25.44) | < 0.0001 |
| 3  | Kuba RH [27] (Treated)     | 344 | 294           | 50               | 98 (33.33%)     | 6 (12%)         | 3.67 (1.48–10.86) | < 0.05 |
| 4  | Kuba RH [27] (Untreated)   | 100 | 50            | 50               | 18 (36%)        | 6 (12%)         | 4.13 (1.36–13.97) | < 0.05 |
| 5  | Al kalaby RF [22]          | 69  | 44            | 25               | 52 (32.27%)     | 5 (20%)         | 4.38 (1.26–17.31) | 0.01 |
| 6  | El-Sayed NM [25]          | 150 | 100           | 50               | 54 (54%)        | 16 (32%)        | 2.49 (1.16–5.47)  | S |
| 7  | Flegr J [26]              | 1320| 301           | 1019             | 6 (46.15%)      | 295 (22.57%)    | 2.94 (0.81–10.30) | 0.012 |
| 8  | El-Henawy AA [24]         | 120 | 60            | 60               | 46 (76.67%)     | 29 (48.3%)      | 3.51 (1.50–8.35)  | < 0.001 |
| 9  | Tian A-L [28]             | 1058| 157           | 901              | 59 (24.79%)     | 98 (11.59%)     | 2.43 (1.66–3.53)  | < 0.001 |
| 10 | Al-Oqaily MA [23]         | 308 | 258           | 50               | 95 (36.82)      | 0 (0%)          | 58.99 (7.35–infinity) | < 0.0001 |

N and n: Number; CI: Confidence interval; RA+: People with rheumatoid arthritis; RA-: People without rheumatoid arthritis; RA+ & T+: People with rheumatoid arthritis and Toxoplasma positive; RA- & T+: People without rheumatoid arthritis and Toxoplasma positive; OR: Odds ratio; NS: Not significant; S: Significant

https://doi.org/10.1371/journal.pntd.0006545.t002
treatment of these diseases with immunosuppressive drugs increases the susceptibility of patients to infections, including toxoplasmosis [6]. Recent treatments for RA patients with anti-tumor necrosis factor-α (TNF-α), which leads to brain toxoplasmosis, are indicative of this issue [27, 38]. On the other hand, some toll-like receptors (TLRs) have been identified in mammals, for which some pathogens act as ligands, and as a result of binding between the TLRs and pathogens different types of immune responses can be induced. Based on reference, *T. gondii* may be used as ligands for TLRs, which can induce inflammatory response [39].

Also, studies show that *T. gondii* increases the expression of interleukin 17 (IL-17) in patients [40], and since this cytokine is involved in the pathogenesis of many autoimmune diseases, including RA [41], a significant relationship between toxoplasmosis and RA can be explained.

RA patients have autoantibodies and rheumatoid factors in their blood [42]. In two studies, these disease activity markers were found to have a significant relationship with toxoplasmosis, especially in high titers [24, 25]. This indicates that *T. gondii* can induce or exacerbate arthritis symptoms [43–45].

Because in the studied articles the relationship of age and sex with the prevalence of toxoplasmosis was not evaluated, we avoided the meta-analysis of these risk factors. In addition, diversity in the quality of studies and methods of measuring antibodies limited the interpretation and analysis of these items. These two issues were the important limitations of our meta-analysis.

Despite the significant relationship found between *T. gondii* infection and RA in this systematic review and meta-analysis study, further studies are needed on the following grounds: 1) the limited sample sizes in the articles, 2) difference in the quality of the reports, 3) diverse methods of measuring anti-parasitic antibodies, and 4) lack of evaluation of various risk factors such as age and gender.

**Conclusions**

One of the most important achievements of our study is that although *T. gondii* infection affects about one-third of the world’s population and possibly causes and exacerbates the symptoms of RA, only few studies have addressed this subject. These studies were conducted only in Latin America, Europe, and few regions of Asia and Africa. Accordingly, further studies are needed to achieve accurate results from other parts of the world. Also, further studies will be necessary to clarify the pathogenesis of *T. gondii* in humans to understand whether *T. gondii* is a cofactor in the development of autoimmune diseases.

**Supporting information**

S1 Checklist. STROBE statement-checklist.

(DOCX)

S2 Checklist. PRISMA 2009 checklist.

(DOC)

**Author Contributions**

**Conceptualization:** Zahra Hosseininejad, Shahabeddin Sarvi, Afsaneh Amouei, Ahmad Daryani.

**Data curation:** Tooran Nayeri Chegeni, Davood Anvari, Reza Saberi, Mitra Sadeghi.

**Formal analysis:** Seyed Abdollah Hosseini.
Investigation: Azadeh Mizani.
Methodology: Zahra Hosseininejad, Afsaneh Amouei, Seyed Abdollah Hosseini.
Project administration: Ahmad Daryani.
Software: Seyed Abdollah Hosseini.
Supervision: Mehdi Sharif.
Validation: Shaban Gohardehi.
Visualization: Zahra Hosseininejad, Afsaneh Amouei, Ahmad Daryani.
Writing – original draft: Zahra Hosseininejad.
Writing – review & editing: Afsaneh Amouei, Ahmad Daryani.

References
1. Robert-Gangneux F, Darde M-L. Epidemiology of and diagnostic strategies for toxoplasmosis. Clinical microbiology reviews. 2012; 25(2):264–96. https://doi.org/10.1128/CMR.05013-11 PMID: 22491772
2. Mizani A, Alipour A, Sharif M, Sarvi S, Amouei A, Shokri A, et al. Toxoplasmosis seroprevalence in Iranian women and risk factors of the disease: a systematic review and meta-analysis. Tropical medicine and health. 2017; 45(1):7. https://doi.org/10.1186/s41182-017-0048-7 PMID: 28413330
3. Montoya JG, Liesenfeld O. Toxoplasmosis. The Lancet. 363(9425):1965–76. https://doi.org/10.1016/S0140-6736(04)16412-x PMID: 15194258
4. Hill D, Dubey J. Toxoplasma gondii: transmission, diagnosis and prevention. Clinical microbiology and infection. 2002; 8(10):634–40. PMID: 12390281
5. Wilking H, Thamm M, Stark K, Aebscher T, Seeber F. Prevalence, incidence estimations, and risk factors of Toxoplasma gondii infection in Germany: a representative, cross-sectional, serological study. Scientific reports. 2016; 6:22551. https://doi.org/10.1038/srep22551 PMID: 26936108
6. Flegr J, Prandota J, Sovičková M, Israili ZH. Toxoplasmosis—a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. PloS one. 2014; 9(3):e90203. https://doi.org/10.1371/journal.pone.0090203 PMID: 24662942
7. Daryani A, Sharif M, Dadimohammad Y, Souteh MBH, Ahmadpour E, Khalilian A, et al. Determination of parasitic load in different tissues of murine toxoplasmosis after immunization by excretory–secretory antigens using Real time qPCR. Experimental parasitology. 2014; 143:55–9. https://doi.org/10.1016/j.exp哪怕是.2014.05.008 PMID: 24852216
8. Montoya JG, Jordan R, Lingamneni S, Berry GJ, Remington JS. Toxoplasmic myocarditis and polymyositis in patients with acute acquired toxoplasmosis diagnosed during life. Clinical infectious diseases. 1997; 24(4):676–83. PMID: 9145743
9. Balleeri E, Cutolo M, Accardo S. Adult-onset Still’s disease associated to toxoplasma gondii infection. Clinical rheumatology. 1991; 10(3):326–7. PMID: 1790646
10. Vass M, Kullmann L, Csoka R, Magyar E. Polynenisynovitis caused by Toxoplasma gondii. Bone & Joint Journal. 1977; 59(2):229–32. PMID: 873984
11. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003; 423(6937):356–61. https://doi.org/10.1038/nature01661 PMID: 12748655
12. Prasad SK, Vassiliou VS. Rheumatoid Arthritis: Mapping the Future. JACC: Cardiovascular Imaging. 2015; 8(6):537–9. https://doi.org/10.1016/j.jcmg.2014.12.024 PMID: 25997192
13. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. New England Journal of Medicine. 2011; 365(23):2205–19. https://doi.org/10.1056/NEJMra1004965 PMID: 22150039
14. Shapira Y, Agmon-Levin N, Selmi C, Petriková J, Barzilai O, Ram M, et al. Prevalence of anti-toxoplasma antibodies in patients with autoimmune diseases. Journal of autoimmunity. 2012; 39(1–2):112–6. https://doi.org/10.1016/j.jauto.2012.01.001 PMID: 22297145
15. Shapira Y, Agmon-Levin N, Shoethey S. Defining and analyzing geoparasitology and human autobody. Journal of autoimmunity. 2010; 34(3):J168–J77. https://doi.org/10.1016/j.jauto.2009.11.018 PMID: 20034761
16. Fischer S, Agmon-Levin N, Shapira Y, Katz B-SP, Graelli E, Cervera R, et al. Toxoplasma gondii: bystander or cofactor in rheumatoid arthritis. Immunologic research. 2013; 56(2–3):287–92. https://doi.org/10.1007/s12026-013-8402-2 PMID: 23553228
17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009; 6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS medicine. 2007; 4(10):e296. https://doi.org/10.1371/journal.pmed.0040296 PMID: 17941714

19. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002; 21(11):1539–58. https://doi.org/10.1002/sim.1186 PMID: 12111919

20. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Brmj. 1997; 315(7109):629–34. PMID: 9310563

21. Daryani A, Hosseininejad Z, Amouei A. Relationship between toxoplasmosis and rheumatoid arthritis: A systematic review and meta-analysis: PROSPERO; 2017 [cited 2017].

22. Alkalaby RF, Sultan B, AL-Fatlawi S, AbdulKadhim H, ROF. Relationship between Toxoplasma gondii and Autoimmune Disease in Aborted Women in Najaf Province. Karbala J Med. 2016; 9(1):6.

23. Al-Oqaily MA, kasim Al-Ubadii I. Prevalence of toxoplasmosis of in Iraqi rheumatoid arthritis patients and detection levels of and TGF-β chemokines during infection. I.J.S.N. 2017; 8(4):824–829.

24. El-Henawy AA, Hafez EAR, Nabih N, Shalaby NM, Mashaly M. Anti-Toxoplasma antibodies in rheumatoid arthritis patients treated with methotrexate. Iraqi J Sci. 2014; 55:1535–40.

25. Tian A-L, Gu Y-L, Zhou N, Cong W, Li G-X, Elsheikha HM, et al. Seroprevalence of Toxoplasma gondii infection in arthritis patients in eastern China. Infectious diseases of poverty. 2017; 6(1):153. https://doi.org/10.1186/s40249-017-0367-2 PMID: 29065914

26. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. The American journal of managed care. 2012; 18(13 Suppl):S295–302. PMID: 23327517

27. Dubey JP, Beattie C. Toxoplasmosis of animals and man: CRC Press, Inc.; 1988.

28. Dardé M-L. Toxoplasma gondii, “new” genotypes and virulence. Parasite. 2008; 15(3):366–71. https://doi.org/10.1051/parasite:2008153366 PMID: 18814708

29. Shapira Y, Agmon-Levin N, Shoenfeld Y. Geoepidemiology of autoimmune rheumatic diseases. Nature Reviews Rheumatology. 2010; 6(8):468–76. https://doi.org/10.1038/nrrheum.2010.86 PMID: 20567251

30. Goekce C, Yazar S, Bayram F, GÜNDOĞAN K. Toxoplasma gondii antibodies in type 1 diabetes mellitus. Turkıye Klinikerı Journal of Medical Sciences. 2008; 28(5):619–22.

31. Majidiani H, Dalvand S, Daryani A, Galvan-Ramirez MdIL, Foroutan-Rad M. Is chronic toxoplasmosis a risk factor for diabetes mellitus? A systematic review and meta-analysis of case-control studies. Brazilian Journal of Infectious Diseases. 2016; 20(6):605–9. https://doi.org/10.1016/j.bjid.2016.09.002 PMID: 27768900

32. Wilcox M, Powell R, Pugh S, Balfour A. Toxoplasmosis and systemic lupus erythematosus. Annals of the rheumatic diseases. 1990; 49(4):254–7. PMID: 2339908

33. Kaňková Š, Prochazkova L, Flegr J, Calda P, Springer D, Potlikova E. Effects of latent toxoplasmosis on autoimmune thyroid diseases in pregnancy. PloS one. 2014; 9(10):e110878. https://doi.org/10.1371/journal.pone.0110878 PMID: 25350671

34. Cren J, Bouvard B, Crochette N. Cerebral toxoplasmosis and anti-TNFα: a case report. IDCases. 2016; 5:40–2. https://doi.org/10.1016/j.idcr.2016.06.006 PMID: 27478763

35. Ali T, Kaitha S, Mahmoud S, Ftesi A, Stone J, Bronze MS. Clinical use of anti-TNF therapy and increased risk of infections. Drug, healthcare and patient safety. 2013; 5:79. https://doi.org/10.2147/DHPS.S28801 PMID: 23569399
40. Guiton R, Vasseur V, Charron S, Torres Arias M, Van Langendonck N, Buzoni-Gatel D, et al. Interleukin 17 receptor signaling is deleterious during Toxoplasma gondii infection in susceptible BL6 mice. The Journal of infectious diseases. 2010; 202(3):427–35. https://doi.org/10.1086/653738 PMID: 20575661

41. Gaffen SL. The role of interleukin-17 in the pathogenesis of rheumatoid arthritis. Current rheumatology reports. 2009; 11(5):365–70. PMID: 19772832

42. Nielen MM, van Schaardenburg D, Reesink HW, Van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis & Rheumatology. 2004; 50(2):380–6. https://doi.org/10.1002/art.20018 PMID: 14872479

43. Abbasi J. To prevent rheumatoid arthritis, look past the joints to the gums. Jama. 2017; 317(12):1201–2. https://doi.org/10.1001/jama.2017.0764 PMID: 28273301

44. Li S, Yu Y, Yue Y, Zhang Z, Su K. Microbial infection and rheumatoid arthritis. Journal of clinical & cellular immunology. 2013; 4(6):174. https://doi.org/10.4172/2155-9899.1000174 PMID: 25133066

45. Bennett JC. The infectious etiology of rheumatoid arthritis. Arthritis & Rheumatology. 1978; 21(5):531–8. https://doi.org/10.1002/art.1780210507