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**Impact of *Streptococcus pyogenes* infection in susceptibility to psoriasis: A systematic review and meta-analysis**

Yousefi A *et al*. *Streptococcus pyogenes* infection and psoriasis

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**Abstract**

BACKGROUND

Psoriasis is one of the most common chronic systemic diseases, mainly appearing as lesions on the skin and joints, and is associated with a high mortality due to a lack of standard treatment. The exact mechanism of this disease is not fully understood, but the inflammatory response and dysregulation of the immune system are the most important molecular processes that trigger this disease. The skin microflora is one of the main factors involved in inducing, maturing, and dysregulating the immune system, which may underly the development of psoriasis.

AIM

To determine the impact of *Streptococcus pyogenes* (*S. pyogenes*) infection and susceptibility to psoriasis using available case-control studies.

METHODS

In this study, we conducted a comprehensive literature search using PubMed, Scopus, Web of science, and Google scholar databases to obtain all available relevant studies on the association between *S. pyogenes* and psoriasis. We pooled the data using Comprehensive Meta-analysis software to investigate the role of *S. pyogenes* infection in the development of psoriasis. The probable connection between *S. pyogenes* and susceptibility to psoriasis was assessed using the odds ratio (OR) with corresponding 95% confidence intervals (CIs).

RESULTS

Data from 781 cases were evaluated in this study. Our results showed that the rate of infection with *S. pyogenes* in psoriatic patients and healthy individuals was 33.4% (95%CI: 27.8-39.6) and 16.2% (95%CI: 9.7-25.9), respectively. *S. pyogenes* infection significantly increased the risk of psoriasis (OR: 6.58; 95%CI: 3.64-11.87; *P* = 0.001).

CONCLUSION

*S. pyogenes* infection can significantly increase the risk of psoriasis. Thus, infection with *S. pyogenes* is a risk factor for the initiation and development of psoriatic events.

**Key Words:** Meta-analysis; Psoriasis; *Streptococcus pyogenes*; Infection; Susceptibility

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**Core Tip:** Currently, the causes of autoimmune diseases are being seriously considered. According to various studies, both genetic and epigenetic events are reasonable hypotheses for these diseases. Psoriasis is one of the most common autoimmune diseases, and studies conducted in recent decades have shown that infectious diseases caused by *Streptococcus pyogenes* (*S. pyogenes*) (*e.g.*, pharyngitis) may be associated with psoriasis. Based on these studies, autoantibodies produced against streptococcal M12 protein potentially react with human keratin. Statistical analyses in this study showed that infection with *S. pyogenes* increased the risk of psoriasis. Thus, long-term treatment as well as strategies to prevent streptococcal infections will be effective in reducing the risk of psoriasis.

**INTRODUCTION**

Psoriasis is one of the most prevalent multisystem chronic cutaneous inflammatory diseases, usually characterized by lesions including red, dry, itchy, and scaly plaques on the elbows, knees, scalp, and lower back[1]. This disease occurs at all ages and in all parts of the world[1,2]. Based on recent studies, the prevalence of psoriasis is estimated to be 0%-2.1% in children and 0.91%-8.5% in adults[2]. According to the World Health Organization, the prevalence of psoriasis in different countries is reportedly 0.09%-11.43%, and 100 million people worldwide suffer from this disease annually[3]. This disease affects the quality of life of patients, as well as their physical activities, and emotional and social health. Unfortunately, there are no specific and effective treatments for this disease[2-4].

The underlying cause of psoriasis is not yet fully recognized. However, several factors such as smoking, stress, alcohol consumption, genetics, hormones, and infectious agents can affect the susceptibility of people to psoriasis[5]. Meanwhile, the role of infectious agents in the development of psoriasis is prominent, as the microbiome can dysregulate the immune response by stimulating the inflammatory process, which triggers the development of autoimmune diseases, particularly psoriasis[1-3]. According to the literature, infectious agents such as *Staphylococcus aureus*, *Streptococcus pyogenes* (*S. pyogenes*), *Propionibacterium acnes*, *Helicobacter pylori*, and *Candida* *spp.* can induce psoriasis[5,6]. In general, *Streptococci* are a predominant microbiome of the human skin and mucous membrane in the healthy population that can cause numerous opportunistic infections[7]. This group of bacteria contains a variety of enzymes, toxins, and superantigens that can stimulate the immune system and cause psoriasis[8].

The possible interaction between previous infection with *S. pyogenesis* and the development of psoriasis remain unknown. In addition, the potential association between *S. pyogenes* and psoriasis has been contradictory in some previously published studies. Hence, for the first time, we conducted this meta-analysis to discuss the molecular aspects of *S. pyogenes* infection in the development of various psoriatic events using available case-control documents.

**MATERIALS AND METHODS**

***Search strategy***

We conducted a systematic search using global databases such as PubMed (available at: https://pubmed.ncbi.nlm.nih.gov/), Scopus (Available at: https://www.scopus.com/search/form.uri?display=basic#basic), Web of Science online databases (available at: https://mjl.clarivate.com/search-results), and Google scholar (available at: https://scholar.google.com/) to collect all of the studies related to the possible association between *S. pyogenes* infection and psoriasis published up to October 2020 without time limits. In this regard, two authors independently searched related articles using the keywords "*Streptococcus pyogenes,*" "*Streptococcus* group A," "*S. pyogenes*” and “psoriasis” according to medical subject heading terms.

***Selection criteria***

The initial documents collected met the criteria for selecting eligible documents. Inclusion criteria were: cross-sectional, case-control, and longitudinal studies on the association between *S. pyogenes* and psoriasis; studies with available full-text; studies on the evaluation of infection frequency in the case and control groups; studies on the assessment of *S. pyogenes* infection using reliable methods; and studies published in the English language. However, studies including review articles, letters and case-reports; Congress articles; duplicate studies; full-text articles with unclear methods and results; and full-text with repetitive samples were excluded. Disagreements between two authors were resolved by a third author.

***Data extraction and quality assessment***

The Newcastle-Ottawa Scale checklist was used to evaluate the quality of eligible articles. Subsequently, the required information such as: the first author, publication year, location of studies, number of patients as well as healthy controls, number of *S. pyogenes* strains in the case/control groups, diagnostic method, and relevant reference number were carefully reviewed by two independent authors. The characteristics of eligible studies are listed in the Table 1.

***Statistical analyses***

The meta-analysis was conducted using Comprehensive Meta-Analysis software version 2.2 (Biostat, Englewood, NJ, United States). First, we assessed the frequency of *S. pyogenes* infection in both patients with psoriasis (case) and healthy individuals groups with 95%CIs. We used the OR with 95%CIs to evaluate the effect of *S. pyogenes* infection on developing psoriasis. Heterogeneity between studies was determined using the statistical inconsistency and Cochrane *Q*-test (*P* < 0.05). The random-effects model, based on the Dersimonian and Laird method, was used when *I2* > 25% and Cochrane *P* > 0.05; otherwise, we used the fixed-effects model. In addition, the presence of publication bias was measured using Begg’s and Egger’s tests[9].

**RESULTS**

In the initial search, 93 articles were selected. In the next step, duplicate studies were deleted, and finally nine articles were recognized as eligible studies and entered used for quantitative analyses (Figure 1).

In this study, the data were evaluated from 781 cases, including 458 psoriatic patients and 323 healthy individuals. Of the studies included, the number of studies was as follows: two in the United Kingdom, two in Iceland, two in Mexico, one in Pakistan, one in Germany, and one in China[10-18]. These studies were conducted during 1991-2008. In these studies, psoriasis was diagnosed using clinical manifestations or pathology examinations, and infection with *S. pyogenes* was diagnosed using tests such as skin CD4+ T cell-producing interferon gamma (IFN-γ), conventional microbiology, antistreptolysin-O (ASO) tetier, anti-beta-hemolytic *Streptococci*, immunofluorescence, and identification of heat shock protein 60 (Table 1).

According to the results of this study, the rate of infection with *S. pyogenes* in psoriatic patients and healthy individuals was 33.4% (95%CI: 27.8-39.6; *P* = 0.001; *I2* = 88.36; *Q* = 60.18; *P* = 0.01; Egger's *P* = 0.33 and Begg’s *P* = 0.45) and 16.2% (95%CI: 9.7-25.9; *P* = 0.001; *I2* = 69.52; *Q* = 22.97; *P* = 0.01; Egger’s *P* = 0.04; Begg’s *=* 0.02), respectively. Moreover, we found that infection with *S. pyogenes* significantly increased the risk of developing psoriasis (OR: 6.58; 95%CI: 3.64-11.87; *P* = 0.001; *I2* = 33.32; *Q* = 11.99; *P* = 0.15; Egger's *P* = 0.38; Begg's *P* = 0.23) (Figure 2).

**DISCUSSION**

Although the exact etiology of psoriasis is not clear, similar to acute rheumatic fever, the onset of clinical manifestations of only type I (but not type II) of psoriasis are associated with pharyngitis caused by *S. pyogenes*[19,20]. However, factors such as hyperproliferation of keratinocytes and dysregulation of the immune system are among the most important aspects that play a key role in the immunopathogenesis of psoriasis. The interaction among the microbiome, keratinocytes, T cell lymphocytes, neutrophils, monocytes, and dendritic cells is highly significant in the development of psoriasis[21,22]. Skin microflora, particularly *Streptococci*, contain several enzymes, toxins, and superantigens that can induce proinflammatory responses, including the production of tumor necrosis factor alpha (TNF-α), IFN-γ, and interleukin 8 (IL-8), as well as production of chemokine receptors, *e.g.*, E-selectin, P-selectin, and CD4 + T cells[23,24]. In addition, recent studies have demonstrated that HLA-Cw\*06 effectively presents *Streptococci* antigens to CD8+ cytotoxic T lymphocytes, leading to a balance distribution between T helper type 1 (Th1) and Th2[23-25]. During chronic inflammation, T-cell lymphocytes are recruited to cutaneous lymph nodes in response to IL-8 and chemokine receptors, and hyperproliferation of keratinocytes also occurs due to high levels of TNF-α and IFN-γ[25,26]. In addition, molecular mimicry between *Streptococci* antigens and auto-antigens of normal skin can also induce the production of antibodies that cross-react with some normal skin auto-antigens. In a study by Muto *et al*[27], it was shown that the serum titers of antibodies against the protein M12 (similar to sub-units of human keratin) of *S. pyogenes* were higher in patients with psoriasis than in control subjects[27-29]. The presence of *Streptococci* in the chronic psoriasis plaques indicates the role of these bacteria in increasing the risk of psoriasis[30].

For the first time, Shelley *et al*[31] found that intradermal injection of heat-inactivated group A streptococcus (GAS) in the finger of a 39-year-old woman with psoriasis exacerbated psoriasis skin lesions in her finger. Gross *et al*[32] showed that psoriatic patients have a specific cellular immune response against GAS antigen. In their studies, Baker *et al*[10] found that skin T cells in the psoriasis patients are activated and react with M proteins of *S. pyogenes*. In this study, we found that the infection with *S. pyogenes* significantly increased the risk of psoriasis (OR: 6.58; 95%CI: 3.64-11.87). According to the literature, the rate of infection with *S. pyogenes* is high in psoriatic patients. For instance, El-Rachkidy *et al*[33] demonstrated that a large population of psoriatic patients had high immunoglobulin G titers (> 500) against *S. pyogenes*. According to studies by Tervaert and Esseveld[34], McFadden *et al*[35], and Lilja *et al*[36], the rate of *S. pyogenes* infection in the psoriatic patients is reportedly 88%-97%. Kim *et al*[37] showed that the rate of psoriasis in children is significantly associated with ASO serum levels. It seems that *streptococci* can survive as a facultative intracellular pathogen within the epithelial cells of the tonsils, and as a stable source, continuously inject their antigens into the bloodstream and increase the risk of psoriasis[36,38,39]. Based on an *in vitro* study by Ruiz-Romeu *et al*[40] it was demonstrated that *S. pyogenes* could increase the activity of T cell lymphocytes by inducing Th17 responses in patients with guttate psoriasis. In general, according to previous studies as well as our study, on the one hand, infection with *S. pyogenes* increases the risk of psoriasis, and on the other hand, long-term treatment and prevention of its infection reduce the risk of psoriasis.

This study had several limitations including: low sample size, the use of English articles only, publication bias, presence of significant heterogeneity, and lack of subgroup analysis or sensitivity analyses to reduce heterogeneity. However, we showed in this study that the rate of *S. pyogenes* infection in patients with psoriasis was about twice as high as that in healthy individuals. We also showed that infection with *S. pyogenes* could significantly increase the risk of psoriasis.

**CONCLUSION**

*S. pyogenes* can stimulate the skin through its enzymes, toxins, superantigens, and T-cell lymphocytes and increases the risk of psoriasis by dysregulating the immune response. Hence, *S. pyogenes* can be considered a risk factor for psoriasis, and prevention from *streptococcal* infection as well as effective treatment of *S. pyogenes* infections are among the best strategies to reduce the risk of psoriasis.

**ARTICLE HIGHLIGHTS**

***Research background***

Psoriasis is a multifactorial autoimmune disease, and it has been suggested that bacterial infection can contribute to the initiation or development of this disease.

***Research motivation***

We performed this study to discover the association between infection with *Streptococcus pyogenes* (*S. pyogenes*) as potential factors and risk of develop to psoriasis.

***Research objectives***

The objective of this study was to determine the impact of *S. pyogenes* infection and susceptibility to psoriasis using available case-control studies.

***Research methods***

We used a computer-assisted comprehensive literature search to obtain relevant case-control regarding to the possible connection between *S. pyogenes* infection and psoriasis. Finally, the impact of infection with *S. pyogenes* and susceptibility to psoriasis was measured using odds ratio (OR) with 95% confidence intervals (CIs).

***Research results***

The rate of infection with *S. pyogenes* in psoriatic patients *vs* healthy individuals was 33.4% and 16.2%, respectively. Furthermore, there is a significant association between *S. pyogenes* infection and development of psoriasis (OR: 6.58; 95%CI: 3.64-11.87; *P* = 0.001)

***Research conclusions***

Infection with *S. pyogenes* is a risk factor for susceptibility to psoriasis.

***Research perspectives***

Further long-term cohort studies are needed to investigate the relationship between *S*. *pyogenes* infection and psoriasis. Also, studies are needed to evaluate the clinical efficacy of the treatment of *S. pyogenes* infection in decreasing the number of psoriatic events.

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Grade A (Excellent): 0

Grade B (Very good): 0

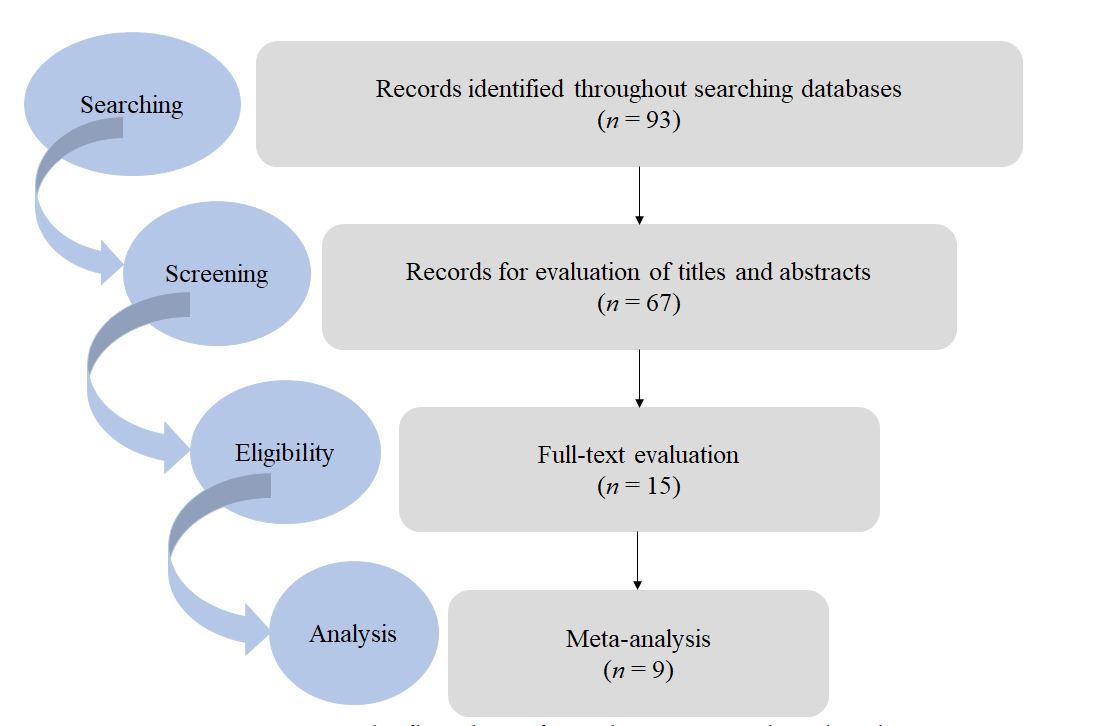
Grade C (Good): C, C, C

Grade D (Fair): 0

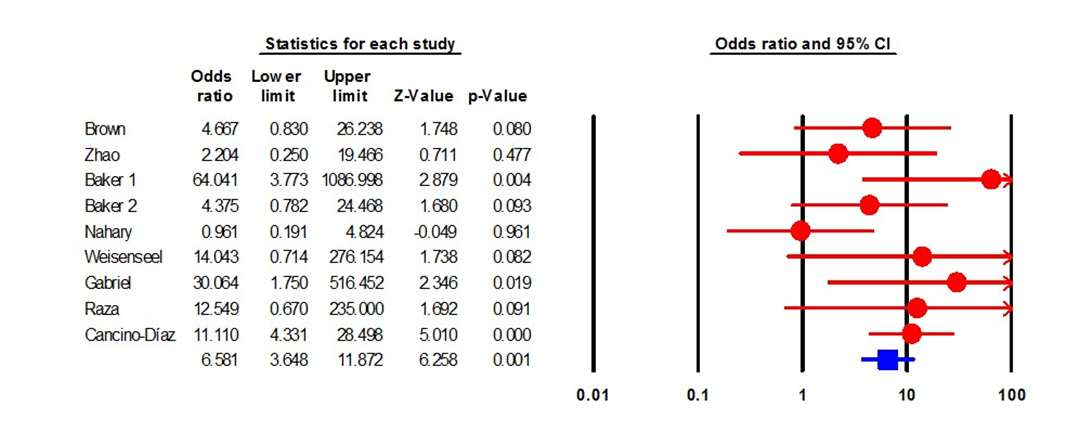
Grade E (Poor): 0

**P-Reviewer:** Muthu S, Sun Q **S-Editor:** Gao CC **L-Editor:** Filipodia **P-Editor:** Li X

**Figure Legends**



**Figure 1 Flowchart of the search strategy and study selection.**



**Figure 2 The probable association between *Streptococcus pyogenes* infection and susceptibility to psoriasis.** CI: Confidence interval.

**Table 1 Characteristics of included studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Location | Total cases | | Number of streptococcal strains | | Diagnostic method | NOS score |
| **Case** | **Control** | **Case** | **Control** |
| Baker *et al*[10], 1991 | Iceland | 78 | 27 | 42 | 0 | Antistreptolysin-O | 8 |
| Baker *et al*[11], 1993 | Iceland | 9 | 18 | 5 | 4 | Skin TCL | 8 |
| Villeda-Gabriel *et al*[12], 1998 | Mexico | 68 | 56 | 14 | 0 | Immunofluorescence | 6 |
| Brown *et al*[13], 2000 | United Kingdom | 13 | 12 | 10 | 5 | Skin TCL | 7 |
| Cancino-Díaz *et al*[14], 2004 | Mexico | 218 | | OR: 11.11; 4.33-28.49 | | Hsp60 | 5 |
| Weisenseel and Prinz[15], 2005 | Germany | 19 | 9 | 8 | 0 | Antistreptolysin-0 | 6 |
| Zhao *et al*[16], 2005 | China | 98 | 42 | 5 | 1 | Conventional | 7 |
| Raza *et al*[17], 2007 | Pakistan | 40 | 40 | 5 | 0 | Conventional | 8 |
| Nahary *et al*[18], 2008 | United Kingdom | 24 | 10 | 7 | 3 | Anti-beta-hemolytic streptococci | 7 |

Hsp60: Heat shock protein 60; NOS: Newcastle-Ottawa scale; OR: Odds ratio; TCL: T-cell lymphoma.



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