Review Article

Possible Association between Benign Migratory Glossitis and Fissured Tongue with Psoriasis: A Meta-analysis

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Abstract

Psoriasis is a chronic inflammatory dermatological disease that affects approximately 2% of the population. It is related to geographic tongue (GT) because both present similar clinical, histopathological, and genetic patterns, suggesting that GT could represent an oral manifestation of psoriasis. The objective of this study is to assess the possible relationship between psoriasis and its possible oral manifestations such as GT and/or fissured tongue (FT). A search for the articles on psoriasis and tongue or oral mucosa was performed in the next electronic databases: PubMed (MEDLINE and Cochrane Library), Web of Science, and Spanish Medical Index (SMI). From 175 potentially eligible articles, 151 were excluded for the several reasons: articles without full-text availability (119) and studies without clinical or usable data (32). Finally, 24 studies were included in this meta-analysis. The data were analyzed using the statistical software RevMan 5.4 (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios (OR) with 95% confidence intervals. Among patients with psoriasis, 8.6% had a GT and 28.2% had a FT. Psoriasis patients were more likely to present both GT (OR: 3.61, $P < 0.001$) or FT (OR: 2.84, $P < 0.001$). Regarding the expression of histocompatibility antigens, patients with psoriasis and GT more frequently expressed type B13 and B57 antigens, whereas controls without psoriasis or GT showed more types B15, B17, B40, B58, C04, Cw6, DR5, and DRw6 antigens. Geographical tongue and FT are most often observed in patients with psoriasis.

Keywords: Benign migratory, fissured, glossitis, mouth, psoriasis, tongue

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Introduction

Psoriasis is a chronic inflammatory dermatological disease characterized by well-circumscribed erythematous squamous lesions, mainly the "plaque" form, which affects approximately 2% of the general population. Despite being a common disorder, its causes remain unknown, and it is attributed to a multifactorial etiology.[1]

Histologically, in the epithelium, parakeratosis, acanthosis, spongiosis, and elongated epithelial ridges can be observed. In the connective tissue, an inflammatory infiltrate of the upper dermis is a usual finding. Polymorphonuclear neutrophil cells migrate and form intraepithelial microabscesses called "Munro abscesses" that are characteristic but not pathognomonic of the disease.[2]

The possible relationship between certain immunological diseases such as Reiter's syndrome, atopic dermatitis or psoriasis, and geographic tongue (GT) has been suggested. GT may present clinical, histopathological, and genetic patterns similar to those of psoriasis, suggesting that it could represent an oral manifestation of this dermatological disease.[3]

GT, also known as benign migratory glossitis, is a condition of unknown etiology found in around 2%–3% of the general population. Clinically, erythematous depapillation areas of different size are observed on the lingual surface surrounded by a whitish border formed by the row of preserved filiform papillae. These areas can disappear and appear in different tongue areas, resembling a map-like appearance on the tongue surface. GT is often seen in conjunction with fissured tongue (FT).[4] This study aimed to assess the association

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between psoriasis and its possible oral manifestations such as GT and/or FT.

Materials and Methods

A search of studies on psoriasis and GT, tongue or oral mucosa was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and the Science Information and Documentation database in Spain (InDICEs-CSIC) that includes the Spanish Medical Index (SMI). Search strategies were developed for each database with a combination of terms from Medical Subjects Headings and free text. The search terms were as follows: "psoriasis" AND ("glossitis, benign migratory" OR "tongue" OR " GT " OR "mouth mucosa" OR "oral mucosa." After this initial search, 281 articles were found (102 in PubMed, 175 in WoS, and 4 in SMI) between the years 1951 and 2020, 106 of them duplicates for having the same title and abstract, which left 175 potentially eligible articles. The article evaluation was carried out independently by two reviewers (ARA and SEO). After, they jointly agreed on the articles to include in this study. The exclusion criteria were as follows: (a) articles without full-text availability (n = 119) and (b) articles without clinical or usable data (n = 32). Finally, 24 articles were included in this study [Figure 1].

Statistical analysis

For the meta-analysis, data were processed with the RevMan 5.4 program (The Cochrane Collaboration, Oxford, UK). For dichotomous variables, the odds ratio (OR) with the Mantel-Haenszel (M-H) Chi-square formula and a 95% confidence interval (95%CI) were used. Heterogeneity was determined according to P values and the Higgins statistic (I^2). In cases of high heterogeneity ($I^2 > 50\%$), the random-effects model was applied. Pearson's Chi-square test was also applied when necessary. A value of $P < 0.05$ was considered the minimum level of significance.

Results

Table 1 presents the prevalence of GT and FT in patients with psoriasis found in 20 studies carried out in 12 different countries.[5-24] 8.6% of psoriasis patients had GT, with a range from 1% in a Finnish study[7] to 19.6% in a NorthAmerican study.[12] On the other hand, 28.2% of psoriasis patients presented FT with a range that was between 6% in studies carried out in the United Kingdom[5] or Israel[6] and 47.5% in a Mexican study.[15]

Figure 2 shows the 11 studies[10,13,15-17,19-24] that examined the prevalence of GT in participants with and without psoriasis. Psoriasis patients were 3.61 times more likely to present GT compared to individuals without psoriasis, found a highly significant association (OR = 3.61, 95% CI: 2.58-5.05, $P < 0.001$).

Eight studies[13,15-17,19-22] analyzed the prevalence of FT in participants with and without psoriasis [Figure 3]. Psoriasis patients had 2.84 times more probability of FT, with highly significant statistical differences (OR = 2.84, 95% CI: 1.88–4.29, $P < 0.001$).

The expression of ten different histocompatibility antigens (HLA) both in participants with GT with and without psoriasis and in controls without GT or psoriasis,

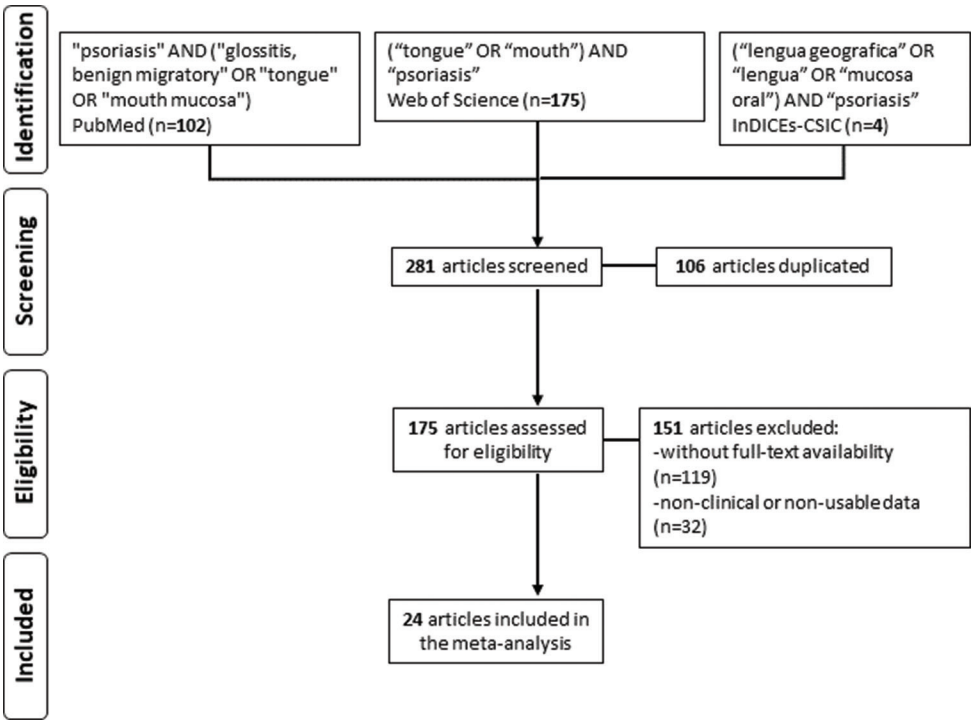

Figure 1: Study flow diagram

Table 1: Prevalence of geographic tongue and/or fissured tongue in patients with psoriasis

Authors	Year	Country	GT prevalence, *n/N* (%)	FT prevalence, *n/N* (%)
Dawson *et al*.[5]	1974	UK	8/117 (6.8)	7/117 (6.0)
Buchner *et al*.[6]	1976	Israel	5/100 (5.0)	6/100 (6.0)
Hietanen *et al*.[7]	1984	Finland	2/200 (1.0)	19/200 (9.5)
Pogrel *et al*.[8]	1988	USA	5/100 (5.0)	7/100 (7.0)
Van der Wal *et al*.[9]	1988	Netherlands	4/70 (5.7)	10/70 (14.3)
Morris *et al*.[10]	1992	USA	21/203 (10.3)	-
Kaur *et al*.[11]	1997	India	21/547 (3.8)	-
Younai *et al*.[12]	1997	USA	9/46 (19.6)	-
Daneshpazhooh *et al*.[13]	2004	Iran	28/200 (14.0)	66/200 (33.0)
Zargari *et al*.[14]	2006	Iran	22/306 (7.2)	30/306 (9.8)
Hernandez-Perez *et al*.[15]	2008	Mexico	10/80 (12.5)	38/80 (47.5)
Costa *et al*.[16]	2009	Brazil	30/166 (18.1)	57/166 (34.3)
Tomb *et al*.[17]	2010	Lebanon	31/400 (7.8)	133/400 (33.3)
Picciani *et al*.[18]	2011	Brazil	25/203 (12.3)	70/203 (34.5)
Germi *et al*.[19]	2012	Italy	49/535 (9.2)	121/535 (22.6)
Darwazeh *et al*.[20]	2012	Jordan	17/100 (17.0)	35/100 (35.0)
Singh *et al*.[21]	2013	India	34/600 (5.7)	272/600 (45.3)
Picciani *et al*.[22]	2015	Brazil	43/348 (12.4)	125/348 (35.9)
Jorge *et al*.[23]	2017	Brazil	21/129 (16.3)	-
Romeo *et al*.[24]	2018	Italy	8/120 (6.7)	-
Total			393/4570 (8.6)	996/3525 (28.2)

n/N (%): Number of cases/total number of individuals (percentage of cases). GT: Geographic tongue; FT: Fissured tongue

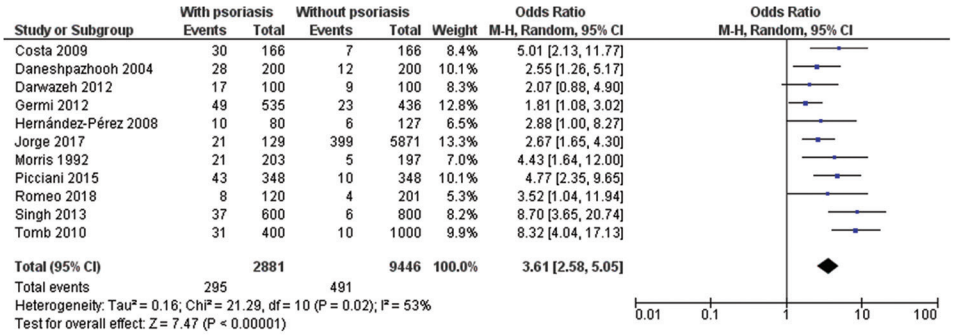

Figure 2: Study data and forest plot graph of the geographic tongue prevalence in participants with and without psoriasis

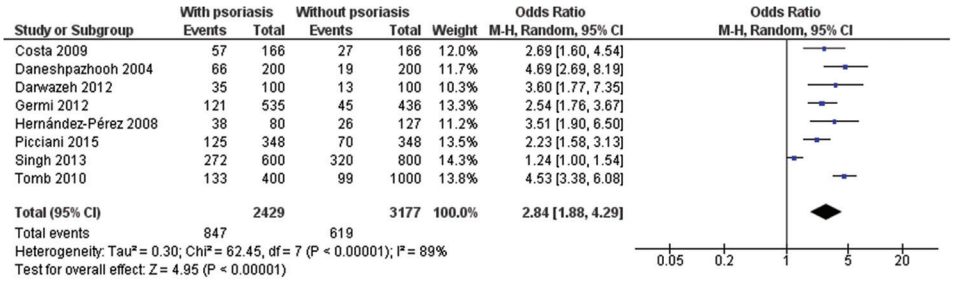

Figure 3: Study data and forest plot graph of the fissured tongue prevalence in participants with and without psoriasis

is shown in Table 2. Regarding HLA-B13, the highest percentage of positive cases was observed in participants with GT + psoriasis and the lowest in controls. A statistically significant relationship ($P = 0.01$) was found when comparing participants with and without GT. In contrast, in the case of HLA-B15, the results are reversed, finding a higher percentage of HLA-B15 positive controls with a statistically significant association ($P < 0.01$). A higher percentage of controls than participants with GT were HLA-B17 positive, with statistically significant differences ($P = 0.03$). The analysis of HLA-B40 in the three groups did not show any statistically significant relationship. The highest percentage

Table 2: Histocompatibility antigens expression according to the presence of psoriasis and/or geographic tongue

HLA antigen	With geographic tongue		Controls†, *n* (%)	*P*‡		
	With psoriasis, *n* (%)	Without psoriasis, *n* (%)		P-T[a]	T-C[b]	P-C[c]
B13[25]						
Positive	4 (44.4)	3 (33.3)	2 (22.3)	0.57	0.01*	0.06
Negative	54 (26.6)	26 (12.8)	123 (61.6)			
B15[26]						
Positive		13 (27.7)	34 (72.3)		<0.01*	
Negative		82 (12.9)	552 (87.1)			
B17[27]						
Positive	6 (23.1)	4 (15.4)	16 (61.5)	0.31	0.75	0.03*
Negative	16 (8.6)	28 (14.9)	143 (77.5)			
B40[26]						
Positive		8 (10.3)	70 (89.7)		0.38	
Negative		87 (14.4)	516 (85.6)			
B57[25]						
Positive	12 (70.6)	0 (0)	5 (29.4)	0.02*	0.61	<0.001*
Negative	46 (23.6)	29 (14.9)	120 (61.5)			
B58[25]						
Positive	4 (16.7)	8 (33.3)	12 (50.0)	0.02*	0.02*	0.75
Negative	54 (28.7)	21 (11.2)	113 (60.1)			
C04[27]						
Positive	5 (9.6)	1 (1.9)	46 (88.5)	0.07	<0.01*	0.62
Negative	17 (10.6)	31 (19.2)	113 (71.2)			
Cw6[25,27]						
Positive	32 (35.6)	19 (21.1)	39 (44.3)	0.29	<0.01*	<0.001*
Negative	48 (14.3)	42 (12.5)	245 (74.2)			
DR5[27,28]						
Positive	4 (1.6)	41 (16.3)	206 (83.1)	<0.01*	0.06	0.07
Negative	18 (4.6)	41 (10.5)	333 (85.9)			
DRw6[28]						
Positive		10 (25.6)	29 (74.4)		<0.01*	
Negative		40 (10.2)	351 (89.8)			

†Participants without psoriasis nor geographic tongue; ‡Pearson chi-square test; *n*: Number of cases; (%): Percentage; [a]P-T: Comparing psoriasis versus geographic tongue; [b]T-C: Comparing geographic tongue versus controls; [c]P-C: Comparing psoriasis versus controls; *Statistically significant. HLA: Histocompatibility antigens

of positivity against HLA-B57 was observed in patients with GT + psoriasis compared to both participants with GT without psoriasis ($P = 0.02$) and in controls ($P < 0.001$).

In the analysis of HLA-B58 antigen, the control group was the most prevalent, found a statistically significant relationship ($P = 0.02$) concerning the participants with GT. Regarding HLA-C04, the highest percentage of positive cases was observed in controls and the lowest, in participants with GT without psoriasis. A statistically highly significant association ($P < 0.01$) was noted when comparing both groups. In the case of HLA-Cw6, a higher percentage of HLA-Cw6 positive controls was proved, with statistically significant differences compared to patients with GT both with psoriasis ($P < 0.001$) and without psoriasis ($P < 0.01$).

A higher percentage of controls than patients with GT + psoriasis were HLA-DR5 positive with a statistically highly significant relationship ($P < 0.01$). The highest percentage of positivity against HLA-DR26 was also found in controls in comparison with participants with GT without psoriasis, finding a statistically highly significant association ($P < 0.01$).

Discussion

In the present review on the possible relationship between GT and/or FT and psoriasis, data from 24 studies have been considered.

Oral psoriasis lesions can be classified into two main groups. The first includes biopsy-proven authentic oral psoriatic lesions with a parallel clinical course with skin lesions. The second comprises most of the oral findings in patients with psoriasis and contains nonspecific lesions such as GT or FT. These tongue conditions are underestimated in the literature, but they deserve more attention due to their high frequency.[13]

The 20 studies that assessed the prevalence of both GT and FT in psoriasis patients[5-24] found increased prevalence in these patients with ranges for GT between 1% and 19.6% and for FT between 6% and 47.5%. The prevalence variances in the

distinct studies may be due to the differences in age, gender, and the different clinical types of psoriasis that affect the populations studied.[20] Furthermore, the precise prevalence of GT can be difficult to determine since the studies were cross-sectional, and this condition presents with the episodes of exacerbation-remission, and there may be periods without apparent lesions.

Some studies do not observe this association between GT and psoriasis, although they do observe this association directly with the FT and inversely with tobacco consumption.[4,7] In contrast, another study concluded that the association of psoriasis with FT was weakly significant ($P = 0.0456$) and that GT was more frequent in male psoriasis patients with more severe forms of the disease.[21]

Costa *et al*.[16] studied 166 patients with psoriasis and 166 controls without dermatological diseases matched by age and sex for the detection of oral lesions. These investigators found that GT and FT were the only oral lesions with statistical correlation with psoriasis compared to other lesions such as denture stomatitis, angular cheilitis, actinic cheilitis, oral lichen planus, traumatic keratosis, fibroma, or hemangioma. However, none of these lesions, including GT and FT, were classified as true oral manifestations of psoriasis since all of them were also observed in the control group.

In this study, psoriasis patients were 3.61 times more likely to present a GT compared to participants without psoriasis, with a highly statistically significant association ($P < 0.001$). The 11 studies[10,13,15-17,19-24] that evaluated the prevalence of GT agreed in highlighting a higher prevalence of GT in the psoriasis patients.

GT presents clinically as one or more erythematous depapillation areas with a white-yellow border formed by preserved lingual filiform papillae. These areas can migrate across the tongue surface and be variable in size. Although its etiology is unknown, it has been associated with various diseases such as atopic disorders, diabetes mellitus, reactive bronchitis, anemia, hormonal disorders, or Down syndrome. Moreover, lesions clinically identical to the GT have been described in patients with Reiter's syndrome or psoriasis.[4]

The characterization of GT as a possible psoriasiform lesion is based on its histological characteristics similar to those of psoriatic lesions. However, this characterization has been a subject of controversy because some investigators do not find this relationship between lesions. Although there are similarities between GT and skin psoriasis, these do not allow GT to be considered a manifestation of psoriasis.[16] The higher frequency of GT in psoriasis patients suggests that both entities are associated conditions, observing histopathological, immunohistochemical, and genetic similarities. However, some researchers do not agree on accepting GT as a manifestation of oral psoriasis since many nonpsoriasis patients present GT too. An important aspect to consider is the family history that reveals genetic factors involved in both diseases. Thirty-eight percent of psoriasis patients and 10% of them with GT reported a family history. Among participants with GT, 27% had a positive family history for this condition and 3% had a family history of psoriasis. Regarding heritability, in patients with psoriasis, 39% of cases is attributed to genetic factors and the remaining 61% to environmental factors. In the case of GT, 37% is due to genetic factors and 63% to environmental factors.[23] Some studies consider GT as a marker of severity of psoriasis since they have observed a higher prevalence of GT in patients with more severe psoriasis, with a direct correlation between its frequency and the severity of the disease.[22]

In the present study, psoriasis patients were 2.84 times more likely to have a FT, with highly statistically significant differences ($P < 0.001$). The eight studies that examined the prevalence of FT both in psoriasis patients and in controls[13,15-17,19-22] found a higher prevalence of this tongue condition in the psoriasis patients.

FT is recognized clinically by the appearance on the lingual surface of anteroposteriorly oriented fissures that often branch and extend laterally. The higher prevalence of FT in psoriasis patients suggests that this condition could be an oral manifestation of psoriasis. However, any conclusion in this regard must take into account that the link between these two conditions is not yet sufficiently proven. Furthermore, FT is a common manifestation in other diseases such as type 1 diabetes, Down syndrome, or Melkersson-Rosenthal syndrome. Just as GT, FT is associated with a genetically inherited trait. All this suggests that the frequent observation of FT in psoriasis patients may be the result of a shared genetic base, an interaction between two genetically different etiological processes or a combination of genetic and pathophysiological interactions.[16]

There seems to be a relationship between FT and the time of onset of psoriasis. Fifty percent of patients with late-onset psoriasis and only 30% of those with an early-onset disease had FT. This could explain the increase in the prevalence of FT with advancing age. Although FT appears to be associated with psoriasis, FT cannot be considered a pathognomonic lesion of the dermatological disease, and new studies are required to clarify this possible relationship. FT is associated with late-onset psoriasis but not with its severity.[20]

In the FT, two main fissure patterns have been described on the lingual surface: central longitudinal and diffuse branched. Unlike what occurs in the general population, in psoriasis patients, the diffuse branched pattern predominates. These distinctive clinical patterns in the FT of patients with and without psoriasis may be a criterion for a suspected diagnosis of the disease.[22]

The expression of different HLA was also analyzed in participants with GT with and without psoriasis, as well as in controls without GT or psoriasis. Susceptibility to psoriasis is related to several genetic factors, the most important of which is found on chromosome 6p21 in the region of

human leukocyte antigens.[25] Various HLA antigens have been associated with psoriasis, mainly the HLA-Cw6.[25,27] According to Gonzaga *et al*.,[27] to consider the GT to be a true manifestation of psoriasis, it should present the same HLA associations as psoriasis, especially an association with the Cw6 antigen. These researchers demonstrated the relevance of HLA-Cw6 expression finding this antigen in 49.1% of psoriasis patients, 43.8% of participants with GT, and in only 12.6% of controls without psoriasis or GT. HLA-B13 is another antigen frequently observed in both psoriasis[25,27] and GT patients,[25,27,28] establishing a possible relationship between both conditions.[25]

Picciani *et al*.[25] found the B15 antigen in 17% of GT participants compared to 19% observed in both psoriasis patients and controls. However, other studies reported greater detection of this antigen in individuals with GT (13.7%) than in controls (5.8%). In the group of GT patients, 77% of them were also atopic patients, suggesting a possible relationship of the B15 antigen with atopy and not with GT.[26] On the other hand, both psoriasis and GT share the detection of the B58 antigen, but not the B57 that is only observed in psoriasis patients.[25] In the present study, the DR5 and DRw6 antigens were more prevalent in the control group compared to the rest of the groups. However, Fenerli *et al*.[28] observed that the prevalence of both antigens was increased in GT patients, although they could not establish any association between GT and other disorders.

At the present time, considering GT and FT as oral manifestations of psoriasis is still controversial because they can also be found in nonpsoriatic patients.[23] In addition, biopsies of these lesions are rarely taken for histopathological study and confirmation of psoriasis.[20] Some require a long-term follow-up of participants with these oral lesions in case they could develop psoriasis in future.[21] However, although these lesions are not pathognomonic for psoriasis, due to their high incidence in patients with psoriasis, they require special attention to try to clarify their possible association with this dermatological disease.[1]

An important limitation in this study was the high heterogeneity found in the results of the prevalence of GT ($I^2 = 53\%$) and/or FT ($I^2 = 89\%$) both in patients with psoriasis and in controls, which requires a careful interpretation of these results.

Conclusions

In the present study, among the patients with psoriasis, 8.6% had a GT and 28.2% had a FT. Psoriasis patients were more likely to have both GT (OR: 3.61, $P < 0.001$) or FT (OR: 2.84, $P < 0.001$) than controls without the disease. Regarding the expression of HLA, patients with psoriasis and GT expressed the B13 and B57 antigens with greater frequency, while, the controls without psoriasis or GT, the antigens types B15, B17, B40, B58, C04, Cw6, DR5, and DRw6.

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Conflicts of interest

There are no conflicts of interest.

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