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The effect of plaque control in the treatment of Oral Lichen Planus with gingival manifestations: a Systematic Review

Fatemah Albaghli,[1] Yuqiao Zhou,[2] Chih-Chung Hsu[3] and Luigi Nibali[4]

[1]Periodontology, Kings College London; [2]Department of Oral Biology, University of Pittsburgh School of Dental Medicine, USA; [3]Department of Stomatology, National Cheng Kung University Hospital, Taiwan; [4]Centre for Host Microbiome Interactions, Kings College, London

Background: Oral lichen planus (OLP) is a chronic autoimmune disease that frequently affects the oral mucosa. Patients with OLP tend to present with plaque accumulation which may further exacerbate the lichenoid lesion, thus plaque control may improve the quality of life of patients. The aim of this review was to test the effect of plaque control on OLP with gingival manifestations. ***Methods***: Systematic review following the PRISMA checklist. A search was conducted through Medline, Embase and the Cochrane Library Database up to March 2020 and complemented by a manual search in some relevant journals. Randomised Controlled Trials (RCTs) reporting plaque interventions and their effects in populations with gingival manifestations of OLP, with a follow-up period of at least 3 months were included. Risk of Bias was assessed using the Cochrane Collaboration Tool in Randomised Trials. ***Results***: The initial search generated 89 sources, resulting in final inclusion of three RCTs following full-text reading. The control groups were asked to continue their regular oral hygiene routine, while test groups received additional tailored oral hygiene advice as the intervention. Two of the included papers had sufficiently similar design to be included in meta-analysis. The oral hygiene intervention was associated with improvements in clinical disease status (Escudier index) and patient-reported outcomes (OHIP-14) from baseline compared with the control group. Differences in visual analogue scores for pain between groups were not statistically different between test and control groups. Two studies were judged to have low risk of bias, while one (not included in meta-analysis) had high risk of bias. ***Conclusion***: Improvements in disease and patient-reported outcomes can occur as a result of oral hygiene instruction in patients with gingival manifestations of OLP.

Keywords*: Oral lichen planus, gingival involvement, plaque control.*

Introduction

Lichen Planus is a chronic autoimmune disease with unclear aetiology (Ismail *et al*., 2007). It may involve the skin and other mucosae, including frequent effects on the oral mucosa, in the variant named Oral Lichen Planus (OLP) (Farhi and Dupin, 2010). The prevalence of OLP is estimated to be between 0.22% and 5% worldwide, and it is most evident in people aged between 30-80 years of age, predominantly females (Cheng *et al*., 2016).

OLP may present as various clinical forms and there are many different classifications in the literature. The 'erosive' and/or 'atrophic' are the most reported symptomatic variants of OLP (Munde *et al*., 2013). Patients may experience warmth, tingling, itchiness, burning sensation, pain, or soreness (Payeras *et al*., 2013). These painful symptoms differ between patients and are quite subjective. They may consequently hinder eating, speech, and proper efficient oral hygiene, thus negatively impacting simple daily activities.

OLP can occur in multiple sites, with the buccal mucosa the most commonly affected site, followed by the tongue and gingiva (Camacho-Alonso *et al*., 2007). When the atrophic form of OLP presents in the gingiva, it is commonly referred to as desquamative gingivitis (Guiglia *et al*., 2007). It may be challenging to diagnose gingival OLP, and some general dental clinicians may be reluctant to treat patients whose gingivae appear different from the typical plaque-induced gingivitis. However, patients with the atrophic variant OLP often present with high levels of plaque (Ramon-Fluixa *et al*., 1999), and might benefit from oral hygiene instruction. A periodontopathogen profile had been identified for OLP compared to healthy non-OLP patients, with subgingival plaque samples from OLP subjects having higher proportions of *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia* and *T. denticola* (Ertugrul *et al.*, 2013). It has been postulated that microorganisms may be responsible for exacerbating the chronic course of OLP (He *et al*., 2017). New evidence supporting the possible role of microbes in this pathogenesis reported that lipopolysaccharide (LPS) from *P. gingivalis* triggers the over-production of cytokines, which have a role in the inflammation process (Wang *et al*., 2018). Thus, motivating the patients to maintain adequate plaque control may improve the severity of the lesions, minimize pain and improve quality of life (Mergoni *et al*., 2019).

The rationale for this systematic review was to assess clinical and patient-centred outcomes following periodontal treatment of OLP, in the form of plaque control. The null hypothesis was that plaque control measures do not improve clinical and patient-reported parameters of OLP.

Method

A systematic review protocol was written in the planning stages and the PRISMA checklist (Moher *et al*., 2009) was followed both in the planning and reporting of the. The protocol was registered with PROSPERO (number CRD42019154391).

Correspondence to: Prof. Luigi Nibali Email: luigi.nibali@kcl.ac.uk

The question addressed was: What is the effect of plaque control on OLP with gingival manifestations? The inclusion criteria were:

- Studies reporting a population with gingival manifestations of OLP
- Randomised control trials reporting plaque control intervention (e.g. hygiene instructions)
- Studies reporting the effect of this intervention on OLP, including patient-centred, laboratory-based and clinical outcomes
- Follow up of at least 3 months after intervention

The exclusion criteria comprised studies not meeting all inclusion criteria

The PICO outline for the review was:

- Population: Oral Lichen Planus patients with gingival manifestations
- Intervention: All forms of plaque control
- Comparison: Compare different forms of plaque control treatments to each other as well as OLP receiving only routine lichen planus treatment

Outcomes were:

- Clinical variables: OLP severity, periodontal assessment parameters (such as changes in bleeding and plaque scores)
- Laboratory variables: e.g. levels of inflammatory cytokines in GCF and/or saliva.
- Patient-centred outcomes: any patient-reported symptoms

The search checklist was in accordance with the Peer Review of Electronic Search Strategies (PRESS) 2015 Guideline Statement (McGowan *et al*., 2015). The electronic databases of Medline, Embase and Cochrane Library Database were searched for studies published up to 2nd March 2020. This was complemented by an Open Grey search and a manual search of including the Journal of Clinical Periodontology (2009-2019), Journal of Periodontology (2009-2019) and Journal of Oral Pathology and Medicine (2009-2019). No language restrictions were applied. References of included papers and of review articles were also checked.

Search terms for the above databases were as follows: MeSH terms used: ((OLP OR oral lichen planus OR oral lichenoid lesion OR oral lichenoid reaction) OR ((OLP OR oral lichen planus OR oral lichenoid lesion OR oral lichenoid reaction) AND (gingival involvement OR desquamative gingivitis))) AND (plaque control OR professional plaque control OR structured plaque control OR oral hygiene OR dental scaling OR dental cleaning OR dental prophylaxis OR toothbrushing OR periodontal debridement). On Open Grey the search was based on: OLP OR oral lichen planus.

Study selection was conducted independently by two reviewers (authors FA and CCH). The initial search consisted of screening relevant papers with titles and abstracts that were potentially suitable. The full texts of potentially suitable papers were then screened. In cases of disagreement about the eligibility of studies, the reviewers tried to reach a consensus or sought the opinion of a third expert reviewer (author LN).

The quality of the included studies was assessed using the Cochrane Collaboration Tool for Assessing Risk Of Bias in Randomised Trials (Higgins and Green, 2011).

Sources were summarised in duplicate in an Excel spreadsheet. Data extraction included study design, inclusion, source of funding, setting, number of patients included and who concluded the study, clinical diagnosis, interventions and any available outcomes. Following this, similarities across included studies were determined. A meta-analysis was considered appropriate for a significant number of studies of similar design, of acceptable quality and low heterogeneity. The effect used in the meta-analyses was the corrected standardized mean difference (Hedges *et al*., 2014). The effect size represented the corrected standardized mean pre- and post-treatment values in experimental groups over the controls after 4 weeks and 20 weeks, respectively (Noble *et al*., 2019). In brief, the effect size was calculated as the post-pre between-group mean difference standardized by the pooled pre-test standard deviations. Meta-analysis using a random-effect model were performed using Metafor package in R software. Heterogeneity was assessed with the chi-square and I^2 tests. The suggested interpretation of I^2 is: 0-40% may represent low heterogeneity, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity and 75%-100% considerable heterogeneity (Higgins *et al*., 2016). Random effects meta-analyses of the selected studies were applied, due to low heterogeneity. Forest plots were produced to represent the difference in outcomes between groups graphically using the patient as the analysis unit. A p value < 0.05 was used as the level of significance. Publication bias was assessed using funnel plots.

Results

The initial search generated 89 articles from Medline, Embase and Cochrane Library Database combined (Appendix 1. Available at http://doi.org/doi:10.18742/RDM01-717). After initial screening, 14 articles were considered potentially suitable by at least one reviewer and qualified for full text screening. No additional sources were found by neither Open Grey nor manual search. After full text reading, 3 sources met the inclusion criteria, while 11 were excluded. The reasons for exclusion were: not a randomized control trial (4 sources), control or interventions did not meet the defined PICO (5), insufficient follow-up time (1) and a duplicate of another included study (1). Every effort was made to obtain relevant missing data by contacting the authors. The Cohen's kappa value for inter reviewer agreement was 0.38 at title and abstract screening level (87.8% agreement) and 1 at second screening (100% agreement).

Table 1 shows the characteristics of the included studies. The studies were conducted in the United Kingdom (n=1) and Italy (n=2). Sample sizes ranged from 60 (Mergoni *et al*., 2019) to 86 patients (Casula *et al*., 2013). The studies were conducted between March 2009 and August 2018 and published between 2013 and 2019. All included studies used histopathological diagnosis of OLP as diagnostic criterion. In two reports (Stone *et al*., 2015 and Mergoni *et al*., 2019), the intervention group received tailored oral hygiene instruction while the control group was simply asked to continue their current routines. The follow-up time for both was 4 and 20 weeks. In the study by Casula and co-workers (2013), the intervention group was included in a 'Prevention and Oral Programme', while the control group was not and the follow-up time was 18 months.

Table 1. Characteristics of included studies

Author Year	*Sample (n)*	*Participants*	*Country*	*Diagnostic Criteria*	*Intervention group*	*Control group*	*Follow-up time*	*Clinical outcomes*	*Patient-reported outcomes*
Stone et al. (2015)	82	Adult patients ≥ 18 years old; willing to consent and able to complete questionnaires; newly referred or under review with a provisional diagnosis of OLP with clinical signs of gingival involvement	UK	Diagnosis of OLP confirmed by biopsy and histopathology and direct immunofluorescence and blood tests where appropriate	Structured oral hygiene instruction using a powered toothbrush and interdental cleaning aids	Asked to continue with their normal plaque control regimen	4 and 20 weeks	PI (Silness and Loe, 1964) and Escudier Index	VAS OHIP-49
Mergoni et al. (2019)	60	Adult patients ≥ 18 years old, non-edentulous	Italy	OLP according to WHO criteria, biopsy proven diagnosis of oral OLP	30 minutes tailored motivation session, with instruction on removal of biofilm. Given manual toothbrushes & dental picks	Asked to maintain their normal oral hygiene habits	4 and 20 weeks	PI (Silness and Loe, 1964) and Escudier Index	VAS OHIP-14
Casula et al. (2013)	86	Age 37-87 years, histopathological diagnosis of OLP (exclusion of nonspecific acanthosis and hyperkeratosis)	Italy	Histopathological diagnosis of OLP	Prevention and Oral Programme (receiving professional and home oral hygiene protocol)	Not included in Prevention and Oral Hygiene Programme	18 months	PI and form of OLP	Burning mouth, reduction of pain & nuisance

All 3 papers had comparable study designs, with tailored oral hygiene advice in the intervention group and no additional plaque control in the control group.

In Stone et al. (2015), the intervention group received structured oral hygiene instructions using a powered toothbrush and interdental cleaning aids. The control group was asked to continue with their normal plaque control regimen without additional advice. The study reported that the intervention reduced plaque more than the control group ($p < 0.001$). Mergoni et al. (2019) reported that their test group received a 30-minutes tailored motivational session with instructions on effective removal of biofilm, while the control group did not receive any advice and was asked to maintain their normal oral hygiene habits. The plaque index reduction was more pronounced in the test (39.3%) than the control group (3.7%) ($p<0.001$). Similarly, participants in the intervention group of Casula et al. (2013) were included in a prevention and oral hygiene programme, while the control group was not. The report described more plaque in the control group although it wasn't clear if this was at baseline and/or follow up. Nor did the report define which plaque index was used. No meta-analysis was possible for plaque scores owing to the different indices used.

Both Stone et al. (2015) and Mergoni et al. (2019) used the Escudier Index to quantify the OLP lesions at baseline and follow-up (although the latter study used a modified version and only included the gingival sextants rather than all intraoral sites). Both reports described significant improvements in the OLP lesions at follow-up in the test rather than control groups. Casula et al. (2013) did not report on the Escudier index. Following receipt of individual data from Stone et al. (2015), meta-analysis including 2 studies (Figure 1) showed significant improvements in the test vs. control group for activity scores at 4 weeks (SMD = 0.83, 95% CI=0.48-1.17, I^2=0%) and 20 weeks (0.91, 95% CI=0.56-1.25, I^2=0%), severity scores at 4 weeks (0.84, 95% CI= 0.50-1.19, I^2=0%) and 20 weeks (0.93, 95% CI= 0.58-1.27, I^2=0%) and site scores at 4 weeks (0.77, 95% CI= 0.43-1.11, I^2=0%) and 20 weeks (1.18, 95% CI= 0.82-1.54, I^2=0%)

Stone et al. (2015) and Mergoni et al. (2019) reported on PROMs using OHIP-49 and Visual Analogue Scales (VAS), and OHIP-14 and VAS respectively. Data for the 14 items included in OHIP-14 were extracted from the original data obtained from Stone et al. (2015). Metanalysis of OHIP-14 data from both sources revealed greater improvement in the test groups at 4 weeks (SMD = 0.41, 95% CI= 0.04-0.78, I^2=19.06) and at 20 weeks (0.35, 95% CI=0.02-0.69, I^2=0%). In terms of the 7 domains of OHIP, Stone et al. (2015) reported statistically significant differences between intervention and control groups at 4 and 20 weeks, in the "functional limitation" (p=0.022, p=0.014), "psychological discomfort" (p=0.007, p=0.002), and "physical disability" domain (p=0.014, p=0.004). Mergoni et al. (2019) also reported on significant differences in the "physical pain" and "physical disability" domains.

VAS scores for pain were similar across groups in both Stone et al. (2015) and Mergoni et al. (2019). Meta-analysis of pain VAS score data (test vs. control) for these studies also showed similar changes in both groups at 4 and 20 weeks (Appendix 2 available at http://doi.org/doi:10.18742/RDM01-717).

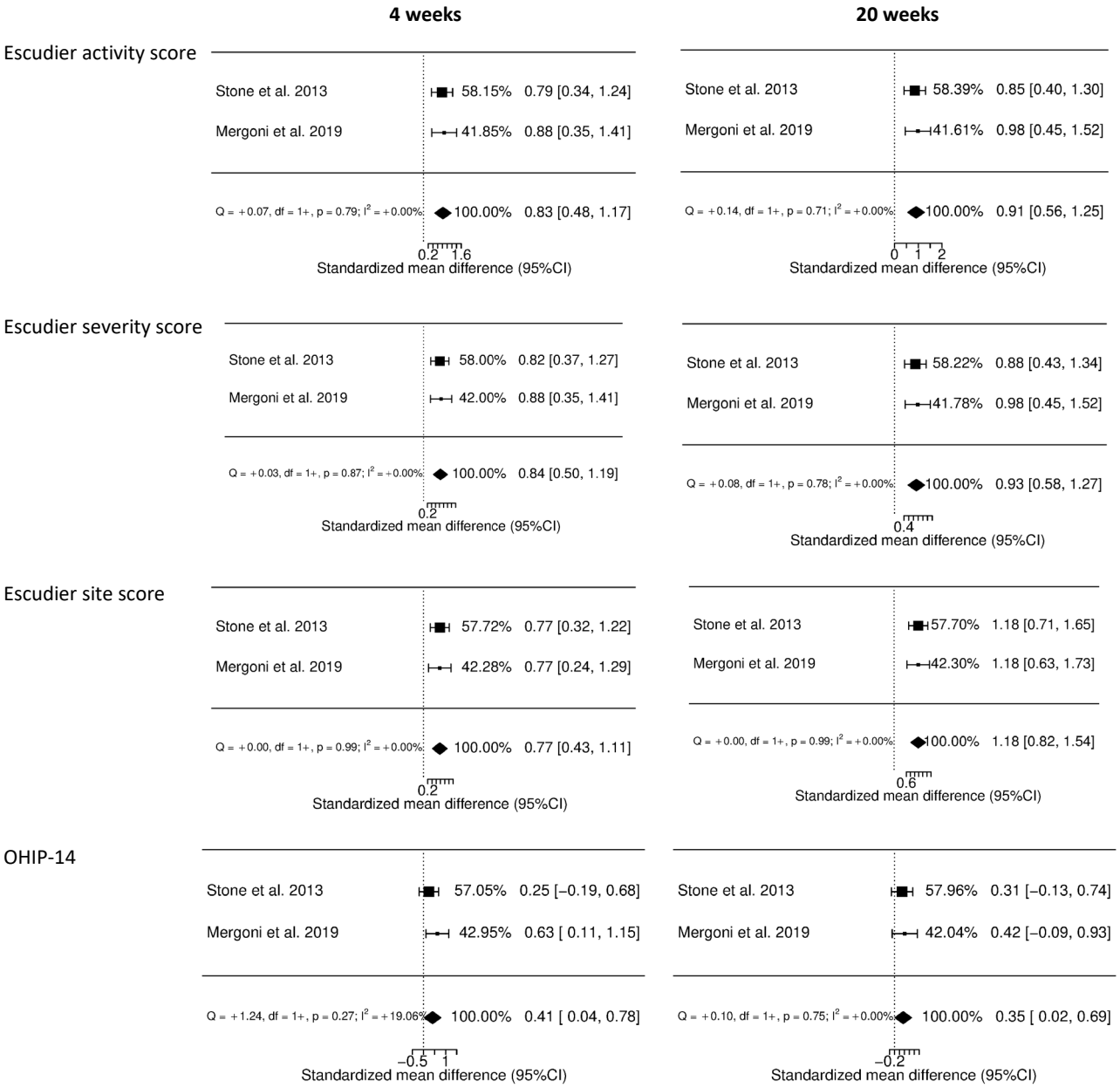

Figure 1. Fixed effects meta-analysis for clinical health status (Escudier index) and oral-health related quality of life (OHIP-14) at 4 and 20 weeks compared with baseline.

Publication bias was assessed using funnel plots (data not reported) (Appendix 3 available at http://doi.org/doi:10.18742/RDM01-717). Both studies appear at the bottom of the funnel due to their small size. All funnels are symmetrical with both studies scattered on either side of the effect line.

No studies reporting laboratory-based outcomes were identified.

Of the 3 included studies, two (Stone *at al*., 2015 and Mergoni *et al*., 2019) were judged to have low risk of bias. Casula et al. (2013) was deemed to have high risk, with details absent on random selection, allocation concealment, attrition bias and reporting bias (Appendix 4, available at http://doi.org/doi:10.18742/RDM01-717).

Discussion

To our knowledge this is the first systematic review of the role of oral hygiene instruction on clinical and patient-reported outcomes of oral lichen planus with gingival manifestations. All three included studies showed reductions in the amount of plaque in the intervention groups. Meta-analysis showed improvement of clinical (Escudier Index) and patient-centred outcomes (OHIP) of oral lichen planus. This intervention and these outcomes are the main focus of this systematic review; none of the included studies reported on laboratory-based outcomes.

The improvement was evident for the clinical severity of the OLP lesions, measured with the Oral Disease Severity Score (ODSS), which assesses the extent and activity of oral mucosal disease (Escudier *et al*., 2007). Although this scoring system includes all the intraoral sites, our site of interest is mainly the 6 gingival sextants. Meta-analysis including two papers showed significant reductions in activity, severity and site scores resulting from oral hygiene advice. However, it is important to note that the Escudier scoring system may not accurately reflect improvements in disease activity, especially if the change observed is small. Such improvement is more likely to be demonstrated in PROMs of pain or quality of life (Escudier *et al*., 2007).

A Cochrane Review of treatments used in OLP concluded that there is a need for standardised and uniform outcome measures to allow interventions to be compared properly (Zakrzewska *et al*., 2005).

Quality of life determined by oral health (OHRQoL) describes a patient's general health and well-being in life, on a day to day basis, in association with an oral pathology (Bennadi & Reddy, 2013). An oral disease may be a cause of chronic stress due to the symptoms accompanying the disease, such as struggling with food selection, swallowing and speaking. Furthermore, episodes of OLP are associated with greater stress and anxiety (Eisen, 2002). The painful forms of OLP can predispose to psycho-emotional manifestations. The persons' perception of the disease, in terms of symptoms, psychosocial impacts and ability to function is thought to reflect the severity of the disease and should be evaluated throughout the course of treatment including at baseline. The use of PROMs is beneficial when diagnosing and treating OLP (Ni Riordain *et al*., 2015). It may also support communication between patient and clinician.

Meta-analysis of included studies show improvements in OHIP-14 scores after targeted oral hygiene advice vs. no intervention, at 4-weeks and 20-weeks. In the studies included in this review, the OHIP domains that showed most significant difference between test and control before and after treatment were the "physical pain" and "physical disability" domains (Mergoni *et al*., 2019; Stone *et al*., 2015). The "physical pain" domain, includes questions regarding painful gums, sore spots in the mouth and discomfort when eating, while the "physical disability" domain reports on inability to brush teeth, and avoidance of eating (Slade *et al*, 1998). The "functional limitation" domain, which includes difficulty with chewing, taste and digestion, was also improved in test vs. control, as was "psychological discomfort", which includes being worried self-conscious and miserable (Stone *et al*., 2015). This is in agreement with a study showing that the most affected domains in patients with OLP were psychological discomfort and social disability (Lopez-Jornet & Camacho-Alonso, 2010). This is a clear indication that distress experienced from OLP has a psycho-social impact on patients' daily lives. These findings are also in agreement with other another RCT (Bianco *et al*., 2019), which reported significant improvement in OHIP scores ($p<0.002$). Casula et al. (2013) did not present OHIP data, but reported participants' "feeling of well-being" in terms of reduction in pain and nuisance in 74% of cases who had received the oral hygiene intervention. It remains to be demonstrated whether the differences shown in this systematic review (0.41 at 4-weeks and 0.35 at 10-weeks) are clinically relevant. Authors of individual papers could report effect sizes and minimally-important differences of OHIP-14 (Jönsson and Öhrn, 2014; Nibali *et al*., 2020), making the results more applicable to clinical practice

The VAS is another commonly used PROM (Ni Riordain *et al*., 2015, Chainani-Wu *et al*., 2008). Stone et al. (2015) and Mergoni et al. (2019) reported similar VAS scores in the intervention and control groups at follow up. This may indicate that pain is not greatly affected by targeted oral hygiene advice. Another possibility may be that the VAS does not capture the "physical pain" domain in the same way as OHIP-14.

Current treatment of OLP is usually directed towards the symptoms to alleviate discomfort. There is a vast array of options, which range from conventional topical or local corticosteroid application, to more novel treatments such as low-level laser therapy (Al-Maweri *et al*., 2017). Another proposed treatment method is a multidisciplinary periodontal-oral medicine approach, which may be the ideal treatment route for gingival involvement OLP patients (Alsarraf *et al*., 2019). A case report by Erpenstein, as early as 1985, suggested that optimal plaque control improved OLP status with gingival involvement. Periodontal treatment in the form of non-surgical and surgical therapy further improved the OLP, which eventually resolved. The rationale behind linking plaque to OLP, is the established finding that mature dental plaque causes gingival inflammation. However, it is currently unclear what effect poor oral hygiene has on oral mucosal surfaces other than the gingivae. There is some evidence that microorganisms may be responsible for exacerbating chronic cases of OLP (Kurago, 2016). Different bacteria have been detected in the saliva of patients with reticular and erosive OLP, compared to normal controls (Wang & van der Waal, 2015). In addition, He et al. (2017) reported that the bacterial structure of OLP on buccal surfaces was significantly different than on healthy sites. It has also been reported that subgingival plaque samples from people with OLP had proportionately more *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia* and *T. denticola* than healthy patients without OLP (Ertugrul *et al*., 2013). It is yet to be confirmed whether this detected dysbiotic state plays a role in the aetiologic mechanism of OLP (He *et al*., 2017). Yet it may be possible to improve the symptoms associated with gingival lichen planus by means of controlled oral hygiene. Management of patients with gingival involvement of OLP improved with the removal of plaque and calculus (Lodi *et al*., 2005). Reduction in the extension of the gingival lichen planus, and the alleviation of subjective symptoms were achieved following oral hygiene procedures (Holmstrup *et al.*, 1990). The effect of sonic versus manual toothbrushing was also investigated in patients with desquamative gingivitis associated with OLP. A sonic toothbrush resulted in improvement of the severity and extension of the lesion in short term, compared to manual toothbrushing (Bianco *et al*., 2018). However, another study suggested potential aggravation in the extent of the OLP lesions by using an electric toothbrush on the affected areas, which they believed lead to minor gingival abrasions (Robinson *et al*., 2005).

The quality of included studies was assessed using the Cochrane Collaboration Tool for Assessing Risk Of Bias in Randomised Trials (Higgins and Green, 2011). Two papers (Stone *et al*., 2015; Mergoni *et al*., 2019) had low risk of bias. Random sequence generation, allocation concealment and blinding and calibration were found to be appropriately carried out and reported. The primary outcomes (OHIP Scores) for both studies were clearly stated. All relevant data were reported on sufficiently and cohesively. However, the report by Casula et al. (2013) had high risk of bias, with missing details about random selection, allocation concealment, attrition bias and reporting bias.

The strengths of this systematic review are the low heterogeneity of the meta-analyses, as well as the observation that it is the first to report on the effect of a tailored oral hygiene advice on the management of OLP with gingival manifestations. The most significant limitation of this systematic review is the small number of studies included in the metanalysis due to the paucity of literature in this area, thus it is difficult to rule out publication bias.

In conclusion, tailored plaque control measures may be effective in improving both the clinical severity of OLP lesions and oral health related quality of life. It may be possible to provide guidelines for general dentists and/or hygienists recommending plaque control as part of initial treatment in patients with OLP before or in parallel to referral to an Oral Medicine department. This can be valuable for improving the care of OLP patients. Additional well-designed randomised control trials may be necessary to further confirm this conclusion and to identify the most effective and practical oral hygiene intervention in the management of OLP.

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