Human Papilloma Virus -6,16 in the Pathogenesis of Oral Lichen Planus -A Systematic Review .


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Abstract
Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease. Though it is considered as autoimmune disease, the exact etiology and treatment is not known yet. Oral lichen planus seems to be not curable and also oral lichen planus has more potency for turning into malignancy. Human papilloma virus (HPV) -6,16 is seem to have significant relation with oral lichen planus. The systematic review is to assess the presence of HPV-6,16 in the pathogenesis of oral lichen planus. Published literature on HPV-6,16 in oral lichen planus from 1990–2016 were searched through PUBMED, MEDLINE and Google. Articles were also selected by a hand search from the relevant journals. Finally, a total of six relevant articles were reviewed. In our review, studies on HPV -16 in oral lichen planus showed 17% positivity and studies on HPV -6 in oral lichen planus showed 8% positivity. Results from the systematic review showed that HPV-6,16 do not have role in the pathogenesis of oral lichen planus. We can conclude from our review that Human papilloma virus -6,16 cannot be detected in oral lichen planus cases. Taking up the oncogenic potential of HPV -6,16 and oral lichen planus as a potentially malignant disorder, more number of studies need to be performed.

Keywords: Assessment; Human papilloma virus -6,16, Oral lichen planus, pathogenesis

INTRODUCTION
Oral lichen planus is common chronic inflammatory disease seen mostly in buccal mucosa, tongue and gingiva, sometimes in palate. Oral lichen planus lesions appear as white plaque like striations, papular or erosive or atrophic or reticular. Oral lichen planus affects middle aged and has more female predilection. It affects about 0.5 to 2.2% of the general population (1). Oral lichen planus is termed as a immunologically mediated mucocutaneous disease. The etiology and pathogenesis of OLP are unknown though several molecular hypotheses have been presented. The etiology of OLP involves the degeneration of the epithelial basal cell layer, induced by cell-mediated immunologic reactions (2). Human papilloma virus belongs to papilloma viridae family. Diameter is 50-500nm and without envelope. HPV's genome is a double stranded DNA. It contains histones and enclosed in protein capsid. Eight open reading frames (ORFs) are encoded by HPV genome. ORF contains three functional parts namely the early region (E), the late (L) region and a long control region (LCR). Early region has role of replication, cellular transformation and it controls viral transcription. Late region is essential for encoding the structural proteins (L1-L2) which is important for virion assembly. Transcription and viral DNA replication is done by long control region. Proteins encoded by early (E) region are E1, E2, E3, E4, E5, E6, and E7. E1 causes viral DNA replication. E6 promotes synthesis of DNA, also prevents differentiation of cells, has interaction with tumour suppression proteins and repair factors, prevents cell differentiation, interacts with tumour suppressor proteins and repair factors; and E7 causes compromise in cell cycle and increases cellular proliferation and also interacts with tumour suppressor proteins. Among the coding proteins, E6 and E7 proteins are causally associated with carcinogenesis and considered as oncogenes. Based on the risk of malignancy HPV are classified as high risk and low risk. Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are high risk due to malignancy potential. Types 6, 7, 11, 16, 32 are seen in Oral papillomas (3-9).

Human papilloma virus (HPV) are mostly associated with proliferative epithelial lesions due to their affinity towards squamous epithelial cells. HPV 16 and 18 by expression of E6 and E7 genes compromise physiological cell cycle control by binding of the related oncoproteins to the tumor suppressor gene products p53 and pRB (10,11). It is also found that HPV infection based on keratinization of tissue, that is keratinized tissue is more resistant to HPV infection (12).

Histologically, oral lichen planus lesions show hyperkeratosis, liquefaction of basal layer, infiltration of lymphocytes in epithelium connective tissue interface. [13,14]. Unknown antigen may play a role for lymphocyte infiltration in this disease. It is also suggested that in OLP apoptosis is triggered by autotoxicotic CD8+ T cells (15). Keratinocyte antigen expression might be altered by exogenous agents. In viral infections, virus acts as cytoplasmic antigen or induce the expression of host cell proteins, which causes altered host cell protein profile. The response of these specific CD8+ T cells is similar to what occurs during a viral infection where a virus can act as a cytoplasmic antigen or induce the expression of host cell proteins, resulting in an altered host cell protein profile (16).

Human papilloma virus (HPV) might play role in pathogenesis of Oral lichen planus (17). HPV-16, HPV-18 and HPV-31, have been found to have an association with Oral lichen planus (18). Therefore, it is of interest to investigate the possibility of viral involvement in the pathogenesis of OLP.

Based on the current evidence, this systematic review analyse Human papilloma virus (HPV)-6,16 in the pathogenesis of Oral lichen planus.
MATERIALS AND METHODS

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES:
The search strategy was in accordance with the Cochrane guidelines for systematic reviews. Articles relevant to the search strategy were identified from search data bases of PUBMED and MEDLINE till the year 2016. Due to limitation of number of articles on Human papilloma virus and Oral lichen planus, no timeline was included for the search. The article search included only those from the English literature. An internet search was also done to obtain the relevant articles of our interest. The title of the articles and abstracts were reviewed. The full text of selected were retrieved and further analysed.

SEARCH METHODOLOGY:
The search methodology applied in PUBMED was using the following keywords:
Search(((((((HPV6) OR Human papilloma virus 6)) AND ((HPV 16) OR Human papilloma virus -16))) AND ((Pathogenesis) OR Pathological process))) AND ((((((((oral lichen planus) OR oral lichen ruber planus)) OR oral mucosal lichen planus)) OR oral autoimmune disease)) OR oral squamo papulous disorder) OR oral papulosquamous disorder) OR Oral mucocutaneous disease)) OR Oral inflammatory disease) OR Oral potentially malignant lesion)) OR Oral precancerous lesion)) OR Oral premalignant lesion) OR Oral white lesion)) OR Oral potentially malignant condition)) OR Oral precancerous condition) OR Oral premalignant condition)

In addition, an internet search was also done using the key words “Oral lichen planus” and “Human papilloma virus-6” and “Human papilloma virus -16”

SELECTION OF STUDIES:
Inclusion criteria:
1. Original studies on Human papilloma virus-6,16 in Oral lichen Planus.
2. Ex vivo studies
3. Studies were the samples are obtained from the patients manifesting the disease in active state.
4. Studies done on tissue samples
5. Studies in English language were included

Exclusion criteria:
1. Studies not done in Oral lichen planus
2. Studies not done in Human papilloma virus -6,16
3. Studies in animals models were excluded
4. Studies done with oral scrapings

DATA EXTRACTION AND OUTCOMES
Once the articles to be reviewed were finalized, data was extracted from each article, tabulated and was verified and interpreted (Fig-1) The outcomes assessed in this review examined and analysed the role of Human papilloma virus-6,16 in the pathogenesis of Oral lichen planus.

Figure 1. Search flow chart
<table>
<thead>
<tr>
<th>S.no</th>
<th>Author</th>
<th>Year</th>
<th>Sample size</th>
<th>Conditions assessed for HPV</th>
<th>HPV Subtypes assessed</th>
<th>Method of HPV detection</th>
<th>Statistical analysis</th>
<th>HPV's detected</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jontell M</td>
<td>1990</td>
<td>20-OLPe</td>
<td>OLPe</td>
<td>HPV-6,11,16,18</td>
<td>Southern blot hybridization and PCR</td>
<td>-</td>
<td>HPV-6,11,16,18</td>
<td>PCR; HPV-6 in 5 OLP cases ,HPV-16 in 3 OLP cases</td>
<td>No statistical analysis done</td>
</tr>
<tr>
<td>2</td>
<td>Christiane Ostwald</td>
<td>2002</td>
<td>112-OSCC,72-OL,12-Chelitis,65-OLP</td>
<td>OSCC,OL,O LP,Chelitis</td>
<td>HPV-6,11,16,18</td>
<td>PCR/Southern Blot Hybridization</td>
<td>Chi-square test</td>
<td>HPV-16,18,6/11</td>
<td>HPV-16 positivity in 16 OL,35 OSCC,2 Chelitis,2 OLP, HPV-6/11 Positivity in 5-OSCC 8-OL,1-Chelitis,5-OLP 6</td>
<td>P value less than 0.005 (significant) Sample sizes vary between conditions</td>
</tr>
<tr>
<td>3</td>
<td>Giuseppina Campisi</td>
<td>2004</td>
<td>71-OLP</td>
<td>OL,OLP</td>
<td>HPV-6,16,18 31,33</td>
<td>PCR and sequencing analysis</td>
<td>Student t Test, Pearson chi Square test</td>
<td>HPV-6,16,18,31,33</td>
<td>HPV-16 In 2 OL,2 OLP, HPV-6 In 1 OLP</td>
<td>HPV-18 Positive in 9-OL,10-OLP HPV-31 in 1 OLP HPV-33 in 1 OL</td>
</tr>
<tr>
<td>4</td>
<td>Pratanporn Arirachakaran</td>
<td>2013</td>
<td>37-OLP</td>
<td>OLP</td>
<td>HPV-16</td>
<td>PCR</td>
<td>Phylogenetic tree construction</td>
<td>HPV-16,33 6,11</td>
<td>HPV-16, In three OLP cases, HPV-6 in 2 OLP cases</td>
<td>HPV-33 In three OLP cases, HPV-11 in 2 OLP cases</td>
</tr>
<tr>
<td>5</td>
<td>Chetan A.pol.</td>
<td>2015</td>
<td>60(30-normal,30-OLP)</td>
<td>Oral lichen planus</td>
<td>HPV-16</td>
<td>Immunohistochemistry</td>
<td>Fisher’s exact test</td>
<td>HPV-16</td>
<td>HPV-16 positivity in 21/30 OLP cases</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Mahnaz Sahebjamiee</td>
<td>2015</td>
<td>40-OLP and 40-normal (saliva and tissue)</td>
<td>OLP</td>
<td>HPV-16,18</td>
<td>Chi square and Fisher's exact test</td>
<td>HPV 16</td>
<td>HPV-16,18,8/40 OLP tissues, 3 saliva samples, 5/40 healthy saliva positive for HPV-16</td>
<td>HPV-18 =8/40 OLP tissues, 3 saliva samples.</td>
<td>P=0.0367 (Significant) Done in specific population Not generalised.</td>
</tr>
</tbody>
</table>
RESULTS

Methods of Review:
The selection and exclusion of the reviewed studies are summarised in 1. The search strategy identified six studies that evaluate Human papilloma virus -6,16 in the pathogenesis of Oral lichen planus. The description of the included studies is shown in Table 3 and that of the excluded studies in Table 4.

Included studies:
Out of the six included studies, detection of Human papilloma virus -16 was evaluated in all 6 studies and Human papilloma virus -6 was evaluated in 4 studies. Due to heterogeneity of the reviewed studies, a meta-analysis could not be performed. Yet a systematic review was conducted and the collected data were tabulated and analyzed.

Table 2. Description Of Excluded Studies

<table>
<thead>
<tr>
<th>S.no</th>
<th>Author</th>
<th>Year</th>
<th>HPV-16 positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jontell M</td>
<td>1990</td>
<td>(3)15%</td>
</tr>
<tr>
<td>2</td>
<td>Christiane Ostwald</td>
<td>2002</td>
<td>(2)3.10%</td>
</tr>
<tr>
<td>3</td>
<td>Giuseppe Campisi</td>
<td>2004</td>
<td>(2)2.80%</td>
</tr>
<tr>
<td>4</td>
<td>Pratanporn Arirachakaran</td>
<td>2013</td>
<td>(3)8.10%</td>
</tr>
<tr>
<td>5</td>
<td>Chetan .A.Pol</td>
<td>2015</td>
<td>(21)70%</td>
</tr>
<tr>
<td>6</td>
<td>Mahnaz Sahebjamiee</td>
<td>2015</td>
<td>(8)20%</td>
</tr>
</tbody>
</table>

Table 2. Description Of Excluded Studies

<table>
<thead>
<tr>
<th>S.no</th>
<th>Author</th>
<th>Year</th>
<th>REASONS FOR EXCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paula Andrea Gabrielli Fregonesi, Debora Barreto Teresa, Roberta Aparecida Duarte, Carlos Benatti Neto, Maria Rita Brancini de Oliveira, and Christiane Pienna Soares</td>
<td>J Histochem Cytochem</td>
<td>Does not satisfy our inclusion criteria. Study was not done in oral lichen planus</td>
</tr>
<tr>
<td>2</td>
<td>F. Elamin, H. Steingrimsdottir, S. Wanakulasuriya, N. Johnson, M. Tavassoli*</td>
<td>Oral Oncology Group, RCS Department of Dental Sciences, King's College School of Medicine and Dentistry, The Rayne Institute, 123 Coldharbour Lane, London SE5 9NU, U.K.</td>
<td>Does not satisfy our inclusion criteria. Study was done in oral squamous cell carcinoma</td>
</tr>
<tr>
<td>3</td>
<td>Syrjanen SM, Syrjiinen KJ, Happonen R-P.</td>
<td></td>
<td>Does not satisfy our inclusion criteria. Study was done in oral squamous cell carcinoma</td>
</tr>
<tr>
<td>4</td>
<td>Stina M. Syrjiinen,* Kari J. Syrjiinen,* and Matti A. Lamberg,*** Kuopio, Finland</td>
<td></td>
<td>Does not satisfy our inclusion criteria. Study was done in oral squamous cell carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>Mravak-Stipetić M1, Sabol I, Kranjić M, Greve M</td>
<td></td>
<td>Does not satisfy our inclusion criteria. Study was done in oral scrapings</td>
</tr>
<tr>
<td>6</td>
<td>Jenice D’Costa a</td>
<td></td>
<td>Does not satisfy our inclusion criteria. Study was done in OSCC</td>
</tr>
</tbody>
</table>

Figure 2
Prevalance of HPV -16 in OLP

<table>
<thead>
<tr>
<th>YEAR OF STUDY</th>
<th>HPV-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>0%</td>
</tr>
<tr>
<td>2002</td>
<td>10%</td>
</tr>
<tr>
<td>2004</td>
<td>30%</td>
</tr>
<tr>
<td>2013</td>
<td>60%</td>
</tr>
<tr>
<td>2015</td>
<td>80%</td>
</tr>
</tbody>
</table>

Figure 3
Prevalance of HPV -6 in OLP

<table>
<thead>
<tr>
<th>YEAR OF STUDY</th>
<th>HPV-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>30%</td>
</tr>
<tr>
<td>2002</td>
<td>5%</td>
</tr>
<tr>
<td>2004</td>
<td>0%</td>
</tr>
<tr>
<td>2013</td>
<td>5%</td>
</tr>
<tr>
<td>2015</td>
<td>0%</td>
</tr>
</tbody>
</table>

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DISCUSSION
Oral Lichen planus is a chronic inflammatory disease that affects the mucus membrane. Oral lichen planus (OLP), presents frequently in the fourth decade of life and affects women more than men in a ratio of 1.4:1[19]. The disease affects 1–2% of the population. It is seen clinically as reticular, papular, plaque-like, erosive, atrophic or bullous types. Intraorally, the buccal mucosa, tongue, and the gingiva are commonly involved although other sites may be rarely affected.[20,21,22] OLP is a chronic inflammatory disease in which the immunopathogenesis involves cell-mediated immune dysregulation. OLP is classified as a potentially malignant lesion of the oral mucosa with a malignant transforming rate of 0–6.25%[23]. Molecular and epidemiological studies suggest that HPV infection in the upper respiratory tract may play a role in the pathogenesis of head and neck tumours[24]. The role of HPV in premalignant lesions has also been studied[25,26]. HPVs are epitheliotropic DNA viruses with more than 150 genotypes. HPV classification has been based on the degree of HPV DNA homology. HPV has been detected in various types of oral benign and malignant lesions[27]. The etiology and pathogenesis of OLP has been the focus of much research.
This systematic review aims at detecting human papilloma virus -6,16 in the pathogenesis of oral lichen planus. This review describing the role of human papilloma virus 6,16 in the pathogenesis of oral lichen planus, in which 6 studies involving 224 subjects were investigated for HPV – 16 presence. Out of these six studies, only 4 studies with 154 subjects were investigated for HPV-6 presence.
Our data suggests that HPV -16 presence in Oral lichen planus is increased over the past few years and HPV-6 presence is seem to be in a same number till now. Results from our study revealed that higher number of studies have been performed on HPV-16 compared to HPV -6 in oral lichen planus.
Jontell .M et al in his study examined prevalence of HPV -6,16 in OLPs (erosive oral lichen planus) and he concluded that HPV may represent one of the risk factors in Oral lichen planus etiology, along with carcinogens like tobacco and alcohol for oral squamous cell carcinoma in erosive oral lichen planus[28]. Christene ostwald et al compared detection rates of HPV -6/11,16 and 18 between oral squamous cell carcinoma ,leukoplakia ,cheilitis and oral lichen planus. He found that no association was seen between HPV and oral lichen planus.[29]
Another study by Giuseppina et al assessed the prevalence of HPV DNA in Oral leukoplakia and Oral lichen planus. He concluded that no association seen between human papilloma virus and oral lichen planus.[30]. Chetan.A.Pol. found significant association between HPV -16 and oral lichen planus[31]. Prataporn Arirachakaran, did study on prevalence of HPV-6,16 in Thai patients. He found that no prevalence of HPV-6,16 in Oral lichen planus patients[32].
This systematic review showed that human papilloma virus (HPV) -6,16 seem to have no role in the pathogenesis of oral lichen planus.
In 1997, the World Health Organization classified Oral lichen planus as potentially malignant disorder.[33,34] and it has transformation rate of about 0-6.25%(35). The major risk factors for oral cancer are tobacco and alcohol consumption. Since long time viruses were also suspected as an etiological factor for oral cancers.
Our systematic review reveals that studies regarding information about HPV genotypes 6,16 in Oral lichen planus is found to be very limited. Lack of adequate number of studies to ascertain HPV-6,16 in Oral lichen planus still persists. Studies to assess the role of HPV -6,16 in pathogenesis of Oral lichen planus need to be done more in future, so that a proper treatment can be given to Oral lichen planus patients.
LIMITATIONS OF THE REVIEW:
We acknowledge that the potential presence of publication bias might have occurred within this review. The number of articles reviewed is minimal. This is due to the limitation of studies available on role of HPV-6,16 in the pathogenesis of OLP. Our search also included publications in the English literature only. Further studies must be performed evaluating the outcome measures that could be useful in evaluating role of HPV-6,16 in the pathogenesis of OLP. This could aid in giving better systematic reviews in future in this field.
CONCLUSION:
This systematic review concludes that HPV-6,16 doesn’t have role in the pathogenesis of Oral lichen planus. From the studies included in the review, predominance for HPV-6,16 were not seen. But still considering the oncogenic potential of HPV -6,16 and Oral lichen planus being a potentially malignant disorder, more number of studies need to be performed, so that we can limit malignant progression and prevent oral squamous cell carcinoma in Oral lichen planus.
IMPLICATIONS IN PRACTICE:
A better knowledge on the role of Human papilloma virus-6,16 in Oral lichen planus - a potentially malignant disorder, which could be helpful in preventing the progression of Oral lichen planus to Oral squamous cell carcinoma. However further studies will be helpful for the practical application of the same.
IMPLICATIONS IN FUTURE RESEARCH:
A better understanding of the Human papilloma virus-6,16 in the pathogenesis of Oral lichen planus. The pathogenesis that are aberrant in the population of patients affected needs to be explored. More studies need to be performed to evaluate the role of HPV-6,16 in Oral lichen planus. This is relevant as the etiology and pathogenesis plays a crucial role, for determining the malignant progression of Oral lichen planus which is a potentially malignant disorder.
CONFLICTS OF INTEREST
None declared
REFERENCES:
30. Giuseppina Campisi, DDS, MScorrespondence email, Lucia C, Palt, Suvarna K.  Ghige and Suchitra R. Gosavi
32. Pratanporn Arirachakaran, Jira Chansangroj, [...], and Yong Poovorawan