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Evaluation of CD40 in tissue of verruca vulgaris: Meta analysis

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Abstract:

Introduction: Verrucae vulgaris is a dome-shaped hyperkeratotic papule that is brought on by HPV, which damages immune response cells known as epithelial cells, which are the first line of defense against infection. CD40, a member of the tumor necrosis factor receptor class, is expressed on keratinocytes, among other types of cells. The immune response against HPV infection is elicited by the ligation of CD40 with its ligand, CD40.

Aim of the study: To evaluate the level of CD40 expression in the tissue of verruca vulgaris infection and its correlation to local characteristics.

Subjects and Methods: The tissue level of CD40 was evaluated in Verruca vulgaris patients in comparison to normal subjects.

Results: After the search and screening, one study was eligible for inclusion in our meta-analysis. Results of the meta-analysis showed that CD40 was higher in patients than controls. The pooled effect estimate showed that tissue levels showed only significance in relation to disease onset. HPV detection was associated with CD40 expression ($r = 0.570$, $p < 0.05$).

Conclusion: Our study may provide evidence of a rise in CD40 levels in verruca vulgaris patients, which plays an important in the immune response elicited against HPVs causing verruca vulgaris.

Key wards: HPV; verruca vulgaris; CD40; warts.

1. Introduction

Verruca vulgaris is a common skin problem, especially in children and adolescents, that commonly affects hands and feet. Verrucae are non-cancerous growths characterized by thickened skin caused by the human papillomavirus (HPV) [1]. Lesions might be single or multiple affecting mainly exposed sites, especially the fingers. Most lesions are caused by HPV types 1, 2, 4, 27, and 57 [2].

In the initial phases of an HPV infection in epithelial cells, the host's innate immune response acts as the primary defense mechanism against the infection. Various cells, such as dendritic cells (DC), Langerhans cells (LC), natural killer cells (NK), natural killer T cells (NKT), and keratinocytes, play crucial roles in facilitating a robust adaptive immune response against HPV infection [3].

2. Subjects and methods

This meta-analysis follows the PRISMA flow diagram and the guidelines of the Cochrane Handbook.

2.1. Eligibility Criteria

Inclusion criteria

- Patients with Verruca vulgaris.
- Sex: both sexes

CD40, which is known as tumor necrosis factor receptor superfamily member 5 (TNFRSF5), is a transmembrane glycoprotein surface receptor. It is present on the cell surface of various cell types, including epithelial cells (ECs) [4].

Typically, when epithelial cells are exposed to CD40 ligation, they respond by upregulating the expression of genes related to leukocyte migration, cell-to-cell signaling, interactions, and processes related to cell death and survival. However, in the presence of HPV, this CD40 signalling is dampened. This attenuation leads to reduced production of chemotactic factors and a lack of enhancement in immune cell migration. Consequently, HPV can evade the immune response more effectively [5].

- Age: 18 to 45

Exclusion criteria

- Patients on any treatment of Verruca vulgaris or had previous treatment for warts.
- Pregnancy and lactation.
- Patients on zinc supplements.
- Patients with other dermatological diseases.

2.2. Information Sources

Our search encompassed a thorough exploration of PubMed, Scopus, Web of Science, and Cochrane CENTRAL databases up until April 2021 to identify pertinent records. Two articles were pivotal in our investigation: the first, titled "CD40 is overexpressed by HPV16/18-E6 positive cervical carcinoma and correlated with clinical parameters and vascular density," shed light on the overexpression of CD40 in HPV16/18-E6 positive cervical carcinoma, establishing a correlation with clinical parameters and vascular density. The second article, titled "CD40-Mediated Amplification of Local Immunity by Epithelial Cells Is Impaired by HPV," delved into how HPV hampers the CD40-mediated amplification of local immunity by epithelial cells, providing critical insights into the immune response evasion mechanisms employed by HPV.

2.3. Search and Study Selection

Interventional and observational studies included people with acne and stress disorders. We screened the included articles in three steps. The initial step involved importing search results from electronic databases into a Microsoft Excel sheet [6], which was facilitated by EndNote

Software [7]. Subsequently, two independent authors undertook the second step, which encompassed a thorough screening of article titles and abstracts imported into the Excel sheet. In the third step, the selected citations from the previous stage underwent a rigorous full-text screening process.

Moreover, to augment the inclusivity of the study, the researchers conducted manual searches within the references of the included papers. This additional step was undertaken to identify any potential studies that might have been inadvertently missed during the electronic database searches, ensuring a comprehensive and exhaustive review of the relevant literature.

2.4. Data Collection

We collected data regarding A) the baseline demographics of the included participants. B) Outcome endpoints, which included BDNF in serum; C). In the third category, data related to the assessment of the risk of bias was meticulously collected. The collection process was executed using Microsoft Excel, ensuring the organization and systematic recording of relevant information about bias evaluation [8].

2.5. Risk of Bias Assessment

Two authors rigorously evaluated the risk of bias among the selected studies by employing

Cochrane's well-established risk-of-bias tool for clinical trials [9]. This meticulous tool facilitated the assessment of crucial aspects such as proper randomization of patients, allocation concealment, and adequate blinding through seven distinct domains [10]. Each domain was meticulously analyzed and categorized as either "low," "unclear," or "high" risk of bias, ensuring a comprehensive evaluation of the methodological quality and reliability of the included studies.

2.6. Main outcomes and measures

All outcomes were formulated before data collection; outcomes included increased levels of tissue CD40 in Verruca vulgaris patients.

2.7. Statistical Analysis

3. Results

Systematic review of 7 articles found that levels of CD40 were elevated in different skin diseases, such as warty lesions associated with

The meta-analysis for this study was conducted using Review Manager software. Our analysis encompassed both continuous and dichotomous outcomes. Continuous data were assessed using mean difference (MD) and 95% confidence intervals (CI), providing a precise measurement of the differences between means across various groups. Dichotomous data, on the other hand, were analyzed using risk ratios (RR) and 95% CI, enabling a comprehensive evaluation of the relative risks associated with specific outcomes. All the data were shown as the mean standard deviation from different independent experiments [11]. The comparisons between the two groups were done by student t-test method and one-way analysis of variance (ANOVA) was handled to approach the distinction between at least three groups. A *P*-value of less than 0.05 is recognized as statistically significant.

HPV, autoimmune disease, and another inflammatory disease.

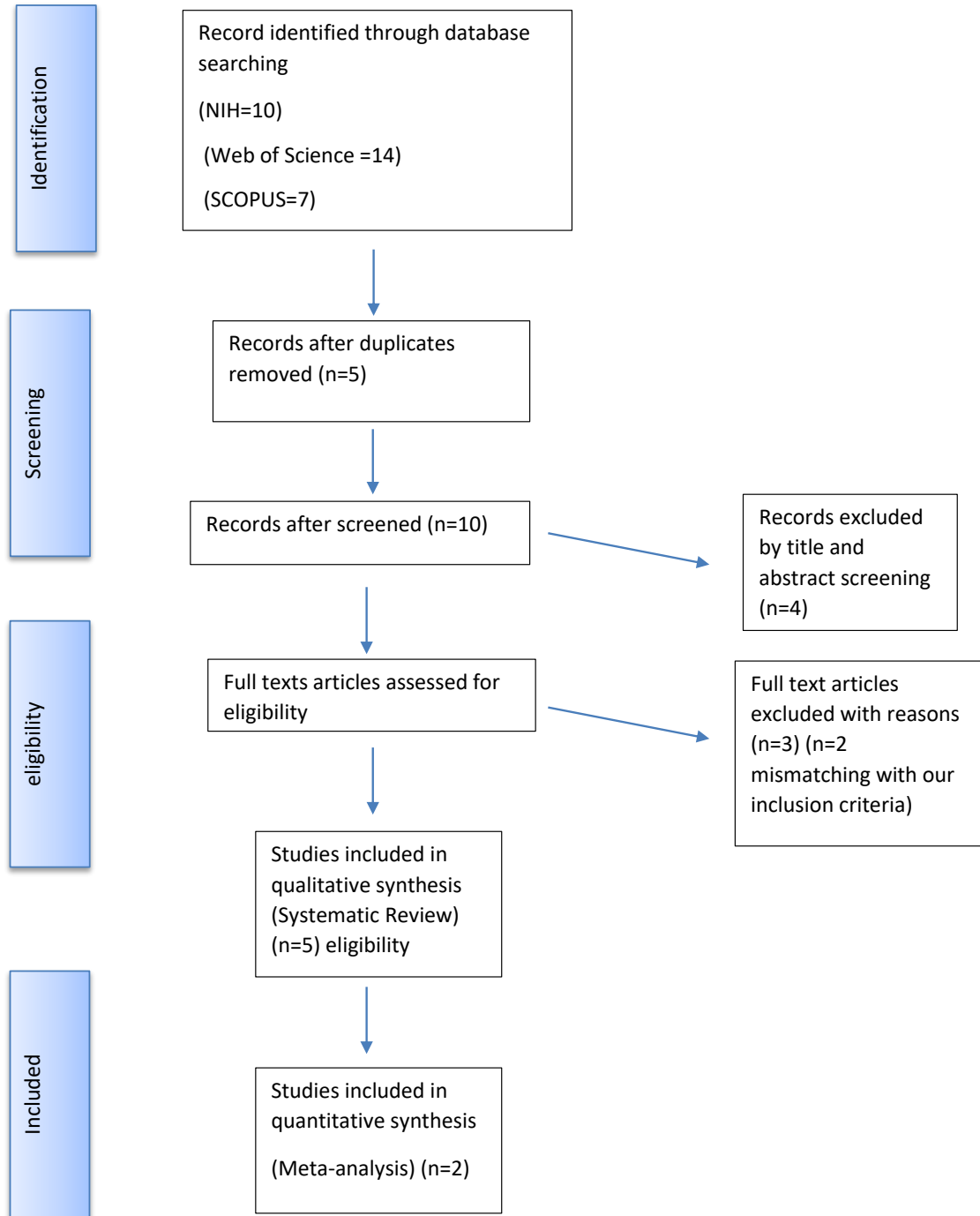


Figure 1: The PRISMA flow diagram of the literature search.

This systematic review and meta-analysis suggest that CD40 levels are associated with immune responses elicited against infection caused by HPV, as seen in Verruca vulgaris. as

this plays an important role in the course and outcome of disease. This study showed that there was a highly statistically significant difference

between patient and controls as regarding CD40 levels in tissue (**Table 1**).

Table 1: Clinical and demographic statistics of the study population.

| Clinical Data | | VV Group | Control | <i>p</i> -value |
|---------------|--------|---------------|--------------|-----------------|
| Age (years) | | 27.0±10.17 | 31.36±9.89 | 0.796 |
| Sex | Male | 10(45.5%) | 11(50%) | 0.678 |
| | Female | 12(54.5%) | 11(50%) | |
| CD-40 | | 954.71±567.67 | 505.34±90.15 | 0.005* |

4. Discussion

Common warts often cure on their own in two months for 42% of patients, six months for 53% of patients, and two years for 65% of patients [12].

The host's innate immune response acts as the initial defense mechanism against infections, including HPV. Various cells, such as dendritic cells (DCs), Langerhans cells (LCs), natural killer cells (NKs), and keratinocytes, play crucial roles in facilitating a robust adaptive immune response against HPV infections. Importantly, these cells have the ability to promote a cytokine-mediated proinflammatory process, establishing a vital link between the innate and adaptive immune responses. This

intricate interplay between innate and adaptive immunity is essential for mounting an effective defense against HPV and other infections [13].

Interaction between CD40 and its ligand CD40L matures and activates DC to produce proinflammatory cytokines and upregulates the immune histocompatibility complex class II and costimulatory molecules CD80 and CD86. These elevated molecules play a significant role in priming CD8+ T cells effectively. They not only prime CD8+ T cells but also stimulate the activated CD8+ T cells, transforming them into cytotoxic effector cells [14].

The dysregulation of the CD40/CD40L interaction can give rise to various clinical

conditions, including autoimmune diseases, intraepithelial malignancies, and inflammatory skin diseases such as psoriasis and subacute systemic lupus erythematosus (SLE) [15].

The interaction of CD40/CD40L in tumor cells could act in two different ways: either it inhibits tumor growth through a group of immunological responses and apoptosis induction or it stimulates tumor growth through different cytokines and growth factors like IL-6, VEGF, and others [16].

A systematic review was done to evaluate the expression of CD40 levels in different skin diseases. A total of 7 studies suggested our finding of the role of CD40 in eliciting different immune responses and showed an elevated level of CD40 in all specimens of psoriasis lesions. Also, CD40 was intensely expressed in squamous cell carcinoma tissue and was found to be higher than in Bowens disease. Another study revealed an increase in CD40 in relation to some diseases, such as atopic dermatitis, which is associated with increased levels of IgE. CD40

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levels were also elevated in the tissues of autoimmune diseases, as seen in SCLE, DLE, and DM. Another study showed increased CD40 expression in the keratinocytes of the oral lichen planus. Two more studies showed upregulation of CD40 in warty lesions caused by HPV.

The meta-analysis of this study revealed a significant increase in tissue level of CD40 in Verruca vulgaris patients as compared to control and increase of CD40 in relation to the rapid onset of disease.

Conclusion

This systematic review and meta-analysis suggest that findings could explain the role of CD40 in eliciting an immune response against infection-causing verruca vulgaris and the relation between CD40 levels and the limited benign course of disease. This study has many limitations, including that it is a case-control study, so it may be liable to be associated with a retrospective nature and don't demonstrate the causation.

Conflicts of Interest: All authors declare they have no conflicts of interest.

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