

THE INFLUENCE OF PEMPHIGUS VULGARIS ON ORAL HEALTH

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SUMMARY

Introduction. Pemphigus is an heterogeneous group of skin and mucosal membranes disease. It is caused by autoantibodies against cell adhesion molecules of keratinocytes. Pemphigus is classified into five major categories: pemphigus foliaceus and IgA pemphigus, pemphigus vulgaris, drug-induced pemphigus, paraneoplastic pemphigus. The aim of this systematic review is analyse the prevalence of periodontal disease in PV patients respect to general population. Furthermore the study evaluates if PV is a risk factor of periodontal disease.

Methods. Two independent reviewers analysed and read 14 articles. After the initial checks the reviewers excluded 12 articles because did not respect the inclusion criteria. The articles are summarized and all data extracted.

Results. The first study of Akman showed a higher CPITN in the study group with a statistical relevance (p value<0.001). The study of Thorat shows a higher PD and CAL in the study group with a statistically significant P value (P value<0.05) Only CAL in the upper arch was higher in the study group with statistical significance (p value 0.0394). The plaque index is higher in the study group with a statistical significance (P value<0.001).

Discussion. Patients with PV can use immunosuppressive drugs and systemic steroids thereby this suppress the immune response. Periodontitis is a disease that affects the tooth supporting structures. It cause the destruction of the alveolar bone and the loss of the teeth. This data shows that PV patients has a high risk to develop periodontitis respect to population. These patients must have a higher frequency of visit by dentist to prevent periodontitis.

Key words: Pemphigus, oral health, periodontal disease.

Introduction

Pemphigus (PM) is a heterogeneous group of skin and mucosal membranes disease. It is caused by autoantibodies that are direct against cell adhesion molecules of keratinocytes. This fact causes loss of adhesion or acantholysis. PM is classified into five major categories: pemphigus foliaceus and IgA pemphigus, pemphigus vulgaris, drug-induced pemphigus, paraneoplastic pemphigus. Only pemphigus vulgaris and paraneoplastic pemphigus have oral features. The word pemphigus means blister or bubble

from a greek word (1). Desmoglein is an important molecule that avoid the adhesion between the keratinocytes. IgG autoantibodies direct against desmogleins cause the loss of adhesion in pemphigus vulgaris. This fact causes acantholysis. Desmoglein-1 is an adhesion molecule that is expressed in the superficial epidermal layers. Desmoglein-3 is situated only in the parabasal and basal layer. Therefore all layer of epidermidis presents Desmoglein-1 and Desmoglein-3. The mucous membranes of the body have a low concentration of Desmoglein-1 (2). The autoantibodies direct against Desmoglein-3 and Desmoglein-1 is a pathognomonic signs of mucocutaneous

pemphigus. Whereas autoantibodies against Dsg-3 promote the presence of lesions only on the mucous membranes. The mechanism of antibody formation is unknown. This pathology has a genetic predisposition, the presence of haplotypes HLA-DR4 and HLA-DR6 give a high predisposition. Recent studies have showed that autoantibodies against 9E Nicotinic acetylcholine receptor caused the acantholysis of skin cells. As regards, cholinergic antagonist can protect the keratinocytes against Desmoglein antibodies and can regress the acantholysis (3). By the results, pemphigus vulgaris usually manifests with oral labial and buccal erosions. The oropharynx and esophagous mucosa can be involved. The principal features are the presence of flaccid blisters and erosions in some areas of the body especially in trunk, groin and face. The pemphigus evolve from erythematous macules and with time into flaccid bullae. In some case involves gingiva and give to patient pain and spontaneous bleeding (4). Nikolsky's sign is a common clinical finding and it is positive when the application of pressure on a blister cause its extension. Whereas when is applied a force on a normal skin and cause the formation of blister, the patient is positive to indirect Nikolsky sign (5). The microscopic analysis shows free fluctuating acantholytic cells in the blister. Intact cells are present in the basal stratum, linked to basal membrane typically called "tombstoning". Inflammatory cells is present in the blister cavity and cause a chronic perivascular inflammation. Direct immunofluorescence shows the deposition of IgG and C3 in a particular way that is called "chicken-wire" (6). PM cause dehydration or secondary systemic infection and was fatal before the introduction of corticosteroids. Patients with PV can use immunosuppressive drugs and systemic steroids thereby this suppress the immune response (7). Periodontitis is a chronic disease that causes the destruction of the supporting structures (8). It causes the destruction of the alveolar bone and the loss of the teeth. Loss of

study that links periodontitis to PV do not helps dentist to treat PV patients. More study links some systemic disease to periodontal disease, for example diabetes, cardiovascular disease. The rationale of the systematic review is to helps dentist to guide PV patients in a control program to prevent the developing of periodontal disease. Furthermore the control of gravity to PD also could mitigate the gravity of symptoms of PV. The aim of this systematic review is the evaluation of the evolution and gravity of periodontal disease in pemphigus patients (9). This study compared the principal periodontal index between the PM patients and the population and evaluate if this pathology is a risk factor for the PD. This create a guideline to dentist to prevent developing of PD. This study uses the PICO methods.

Methods

The study was conducted utilizing the main scientific databases (PUBMED, MEDLINE, and WEB of SCIENCE). The time window considered for the electronic search was from 01/03/2007 to 01/05/2019. The last research on the web was the 01/05/2019. The term "pemphigus" was first combined with "periodontal disease" and then independently with "oral health" using the connector "AND". The web search was assisted by the use of MESH (Medical Subjects Headings). The criteria for this review are described in the PRISMA and by the following flow diagram. Two independent reviewers use the same keywords and analyse the results. The purpose of this review was to answer the following questions using a PICO method (P: patient problem/population; I: intervention; C: comparison; O: outcome):

- 1) In pemphigus patients there are higher incidence of periodontal disease than the population?

- 2) Is there a worsening of the periodontal index in the PM population than population?
- 3) Are there some solution to prevent the progression of periodontal disease?

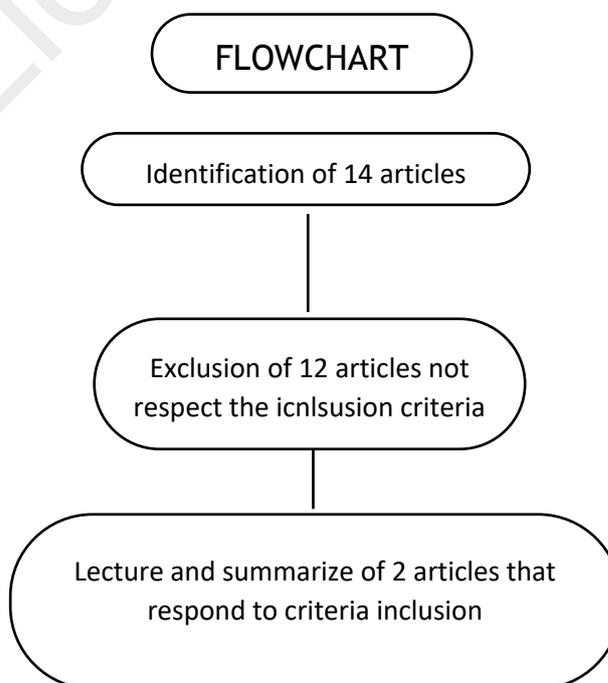
The following inclusion criteria were used: articles in English, human studies, clinical trials. All articles that answered the questions asked by the PICO, were included. The following exclusion criteria were used: articles which did not answer the key questions, case reports, duplicate articles, books, letters to editors and experimental studies. All articles were analyzed by two independent reviewers. All data were extracted. Articles which did not contain data regarding periodontal disease and oral health are excluded. The risk of bias was solved in this way: the articles were collected and read by two independent Authors, the same Authors read and included or excluded the articles independently, and a lack of agreement was resolved by a third Author. All Authors used the same terms and the same in-

clusion and exclusion criteria. (Table 1). The Author reads first read the abstract of all articles, excluded which did not respect the inclusion criteria, after read the complete test of the remains articles. All the reviewers extract the data regarding the periodontal health (PD,CAL,BOP, CPITN). Articles which do not contain the data and the previous index on periodontal health were excluded. All doubts are solved contacting the Author.

Results

Two independent scientists searched the previously mentioned keywords, read the titles and summarized the abstracts of 14 articles. During an initial reading, they excluded the articles that did not respect the topic. Seven articles were excluded because did not treats the periodontal dis-

Table 1 - Flow chart.



ease in the pemphigus patients. Three are excluded because did not treats periodontal disease and do not use the previous index regarding periodontal health. The risk of bias of one articles of the previous three was solved by a third independent reviewer. The third reviewer decided to exclude the articles because do not contain the principla periodontal index. The remaining two articles were read by the two independent reviewers and Authors were contacted to clarify the results. All the two articles respond to PICO answer. Therefore, 2 articles that responded to the key characteristics were selected. Two articles were clinical studies and one was a review. The first article of Akman evaluates the oral health in patients with PV compared to a control group. Furthermore he analyses the periodontal conditions through the Community Periodontal Index of Treatment Needs (CPITN). The study group is composed by 20 patients and the control group by 22 patients. All patients of the study group had a diagnosis of PV based on clinical features and by histopathologic and direct immunofluorescence analysis. The mouth was divided into sextants, each sextant was examined only if there are more than 2 teeth and are not indicated for oral surgery. The parameters were recorded in the 17, 16, 11, 21, 26, 27, 47, 46, 41, 31, 36, 37 and the highest value were recorded for each sextant. The following number were assigned to only sextant: 0, periodontal health; 1,

gingival bleeding; 2, calculus detected during probing; 3, pocket 4- to 5-mm depth; and 4, pocket ‡ 6-mm depth. The periodontal condition and CPITN were assigned to every patients based on the worst sextant. The results of the study showed an high CPITN in the study group with a statistical relevance (p value <0.001) (10). The second study of Thorat analysed the periodontal health and evaluated the correlation between periodontal health and pemphigus vulgaris. The study group were formed by 50 patients and the control group by 50 patients. The diagnosis of PV based on clinical features and by histopathologic and direct immunofluorescence analysis. In the study group patients were excluded who have make periodontal therapy in the last 6 months and who suffered of other systemic disease. The periodontal conditions were analysed by a single dentist with UNC-15 periodontal probe. The CPITN with the same criteria of the previous study is registered. Full mouth, plaque index, bleeding score, probing depth (PD) and clinical attachment level (CAL) were also registered. A statistical analysis evaluated the clinical parameters (Table 2). A PD and CAL were higher in the study group with a statistically significant P value (P value <0.05). Only CAL in the upper arch was higher in the study group with statistical significance (p value 0.0394). The plaque index is higher in the study group with a statistical significance (P value <0.001) (11).

Table 2 - The principal periodontal index.

Akman et al.	p value	Pv group	control group
		Mean age 42.9	Mean age 40.5
	0.001	22 patients: CPITN 2.8 +- 07	22 patients: CPITN 1.0+-0.8
Thorat et al.	p value	50 patients	50 patients
		Mean age 35.2	Mean age 37.0
	0.0146	PD total 4.51+-0.59	PD 3.84+- 0.79
	0.0394	CAL upper arch 3.73+-0.95	2.70+-1.57
	0.001	PI 41.6+-20.4	24.8+-18.3

Discussion

The literature search identified a limited number of studies. The studies revealed a worst periodontal health in the pemphigus patients. Periodontitis is a chronic inflammatory disease caused by multiple aetiological factors. The inflammation due to immune system against some bacteria of the red complex cause the destruction of the components of periodontium. The release of pro-inflammatory cytokines (eg, tumor necrosis factor- α , IL-1, IL-6, IL-8,) and matrix metalloproteinases (eg, gelatinase B) cause bone resorption (12). PM is classified also as an autoimmune disease. The genetic alteration and uncontrolled inflammatory response of pemphigus to various stimuli can lead to rise the CPITN, compared to the rest of population. In addition, the oral mucosa damage could stimulate and perpetuate the autoimmune response for the presence of the antigenic epitopes. Another reason is the presence of oral ulcers and desquamative gingivitis that cause pain and consequently a poor oral hygiene. Desquamative gingivitis has several etiologic factors. Oral lichen planus, cicatricial pemphigoid and pemphigus vulgaris are the most common causes. The gold therapy of pemphigus is systemic corticosteroids, anti-inflammatory drugs, and immunosuppressive agents. Controversial data also exist as regard the role of these drugs in the periodontal health. It represents the gold standard therapy for pemphigus vulgaris and mucosal pemphigus but may alter the host immune against to periodontal bacteria. This therapy can worsen the periodontal conditions by repressing the immune system directed against oral bacteria. Two studies revealed that the therapy has no effects in periodontitis. In contrast, one study shows an improvement of periodontal index such as bleeding index and there are an increasing of gingival recession. In addition, other studies shows an increasing of plaque index during the corticosteroid

therapy compared to remission patients. These observations are very controversial and does not give an important conclusion on the corticosteroid therapy effect on periodontium. The study analyzed reveal a worst periodontal health respect to population. Probably the sample collected by Authors did not have an oral education. According to previous study (13), the socio-economic position influence the periodontal health. Unfortunately, the contact with the Author of the 2 studies by our reviewer, does not reveal the socio economic position of the sample. The worsening of periodontal condition, moreover, are due probably to one or all the following factors. *In primis* the alteration of immune system of PV patients sharpens the PD. The second is due to immunosuppressive drugs used by patients but the results in literature are very controversial. The third factor which probably create bias, are the socio economic position of the sample which contribute to gravity of periodontal disease. Moreover the results, thought with few studies, reveal a worst condition of PV patients respect to general population. All periodontal index analyzed are worst respect to general population. Here the role of dentist is important. The PV patients must have a continuous control program of periodontal condition through professional oral hygiene. Probably the improvement of periodontal index could mitigate the symptoms of PV. In fact in literature is ascertained the link between PD and other systemic disease. The improvement of PD index mitigate the gravity and progression of the principal systemic disease, for example diabetes, cardiovascular disease, tumor etc. In conclusion, common autoimmune mechanisms can worsen the course of periodontal disease. Besides the autoimmune mechanisms, still to be ascertained, the lack of hygiene due to the pain is the main cause of the worsening of the periodontal indexes (14). However, further studies are needed to confirm the presence or absence of interactions between the two pathologies.

Abbreviation list:

PM: Pemphigus Vulgaris

PICO: patient problem/population, intervention, comparison, outcome

CPITN: Community Periodontal Index of Treatment Needs

PD: Probing depth

CAL: Clinical attachment level

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Conflict of Interest:

Authors declare not to have any conflicts of interest.

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