



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# Clinical efficacy of casein phosphopeptide – amorphous calcium phosphate and casein phosphopeptide – amorphous calcium fluoride phosphate and their influence on the quality of life in patients with Sjögren's syndrome

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## SUMMARY

**Introduction/Objective** The purpose of this study was to compare clinical efficacy of casein phosphopeptide – amorphous calcium phosphate (CPP-ACP) and casein phosphopeptide-amorphous calcium fluoride phosphate (CPP-ACFP) with 0.05% NaF, and to assess their influence on the quality of life among individuals with Sjögren's syndrome.

**Methods** Thirty patients were randomized into three groups treated with different remineralizing agents: CPP-ACP, CPP-ACFP, and 0.05% NaF. Oral health was evaluated at the beginning of the study, after 28 days (short-term effects), and after six months. The diagnosis of dental caries was performed using the decayed, missing, and filled teeth (DMFT) / decayed and filled surfaces (DFS) criteria. Enamel demineralization was visually examined using the white spot lesion index (Gorelick). The gingival health was evaluated with the gingival index (Löe–Silness). Assessment of oral hygiene was done using the simplified oral hygiene index (Greene–Vermilion). The Xerostomia Inventory was used to quantify dry-mouth symptoms. The oral health-related quality of life was analyzed using the short form of the Oral Health Impact Profile (OHIP-14).

**Results** During the evaluation period, caries increment was not significant. Considerable regression of white spot lesions was noted in all three experimental groups ( $p < 0.001$ ). No significant improvement in gingival health and oral hygiene was observed. Physical pain was decreased in all three experimental groups, and subjective feeling of dry mouth was reduced in CPP-ACP and CPP-ACFP groups.

**Conclusion** CPP-ACP and CPP-ACFP may reduce the caries activity and relieve the dry-mouth symptoms in patients with Sjögren's syndrome.

**Keywords:** caries; casein phosphopeptide – amorphous calcium phosphate; casein phosphopeptide – amorphous calcium fluoride phosphate; dry mouth; Sjögren's syndrome

## INTRODUCTION

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder, characterized by dysfunction of both salivary and lachrymal glands. Exocrine glands are infiltrated by mononuclear cells (lymphocytic infiltration), causing either compromised or even total failure in secretion of saliva and tears [1, 2]. The variety of symptoms makes SS a complex disease. Pronounced and severe oral dysfunction, disability, and discomfort, defined as oral distress, seem to be the most important factors in a patient's perception of oral health status [3].

The majority of published reports on the oral component of SS focused on dry-mouth symptoms. However, not much attention has been given to the incidence of oral pathology in patients with SS. Despite the fact that the

prevalence of persons with SS is high (1–23 cases per 10,000 inhabitants), while the prevention and early treatment of oral diseases is of the utmost importance in these patients, no caries prevention protocol has been established so far [4]. Usually, topical application of high-concentration fluoride agents is recommended for caries control in patients with salivary hypofunction [5]. However, decreased concentration of calcium and phosphate ions in saliva and plaque of xerostomic patients may be a limiting factor for remineralization driven by topical fluorides [6]. Papas et al. [7] suggested that aggressive fluoride protocols in patients receiving radiation therapy for head and neck cancer could be modified with adjusting the level of phosphate and calcium ions in remineralizing agents.

One of the most studied calcium phosphate-based nanotechnologies is casein

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phosphopeptide – amorphous calcium phosphate (CPP-ACP). This formulation localizes effectively at the surface of tooth enamel and enables a long enough retention of phosphate and calcium ions at the site where remineralization is wanted [6].

The purpose of the present study was to compare clinical efficacy of CPP-ACP and casein phosphopeptide – amorphous calcium fluoride phosphate (CPP-ACFP) containing pastes with 0.05% NaF oral rinse, and to evaluate the influence of these agents on dry-mouth symptoms and oral health-related quality of life in patients with SS.

## METHODS

This longitudinal observational study was approved by the Ethics Committee of the School of Dental Medicine, University of Belgrade (document 36/30). The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

The patients who were referred to the Clinical Centre of Serbia, Institute of Rheumatology and the Clinic of Allergology and Immunology were participants in this study. Dental examination was performed on thirty patients at the School of Dental Medicine of the University of Belgrade. One dentist performed the first dental exam making random treatment assignments. A random number table was used to randomize patients into three groups treated with different agents ( $n = 10$ ): 1) 10% CPP-ACP (Tooth Mousse, GC Int Corp, Tokyo, Japan), 2) 10% CPP-ACP and 0.9 mg/g fluoride in CPP-ACFP (MI Paste Plus, GC Int), and 3) 0.05% NaF (Curasept ADS 205, Curaden International AG, Kriens, Switzerland). The sample size was calculated with 80% power at the 5% significance level, assuming the 5% dropout rate. The total sample size for the three groups was calculated to be 30 participants. A detailed description of the study material and methods has been published previously [8].

An assessment of oral health status of each participant was conducted at the beginning of the study, after 28 days (short-term effects) and after a six-month use of remineralizing agents. The complete oral exam was performed by two trained dentists, blinded for treatment allocation, using a dental mirror and explorer. The WHO criteria were used for the diagnosis of dental caries [decayed, missing, and filled teeth (DMFT) / decayed and filled surfaces (DFS)] [9]. Enamel demineralization was visually examined using the white spot lesion index (WSL – Gorelick) [10]. The gingival health was evaluated with the gingival index (GI – Löe–Silness) [11]. Assessment of oral hygiene was done using the simplified oral hygiene index (OHI – Greene–Vermilion) [12].

During the investigation, the patients were interviewed about their dietary and oral hygiene habits. The dietary habits questionnaire comprised nine questions about the number of main meals, number and type of cariogenic snacks, use of chewing gum, frequency of beverage intake, and the type of sweetener. The oral hygiene habits analysis included six questions related to regularity of tooth

brushing, oral hygiene devices and products, and fluoride uses.

To compliment clinical examination, a self-rating of oral health and its influence on life in general was evaluated. Patients rated their oral health as: excellent, very good, good, fair, or poor. Self-assessed impact of oral health on life in general was recorded as follows: not at all, very little, some, a lot, and very much. The Xerostomia Inventory (XI) was used for measuring xerostomia symptoms [13]. Answers were coded as follows: 1 = never, 2 = hardly ever, 3 = occasionally, 4 = fairly often, and 5 = very often. Oral health-related quality of life was analyzed using a short form of the Oral Health Impact Profile (OHIP-14) [14]. The answers were marked as follows: 0 – never, 1 – hardly ever, 2 – occasionally, 3 – fairly often, and 4 – very often. Results for XI and OHIP-14 were obtained by summing up scores for each question. The prevalence of impacts was estimated by identifying individuals who answered with 'fairly often' and 'very often' [15].

Descriptive statistical analyses were primarily implemented. Kruskal–Wallis test and Wilcoxon test were used to analyze differences within the same treatment group during the experimental period. For the comparisons of frequency distributions, Fisher exact test and  $\chi^2$  test were used. The significance level of  $p < 0.05$  was used. Statistics software package SPSS was utilized for data processing.

## RESULTS

The study included 27 female and three male volunteers aged 15–65 years (mean  $39.7 \pm 16.6$  years). Twenty-two (73%) participants came from urban communities, six (20%) persons were from peri-urban areas, and two (7%) were from rural areas. Education of participants was not equal: three (10%) patients completed primary school, 16 (53%) completed secondary school, five (17%) had a university degree, while six (20%) belonged to the category "pupil/student."

All patients experienced SS symptoms from at least six months to 25 years (average  $5.7 \pm 5.6$  years). Hypertension was present in four patients, diabetes in three, and both conditions in one patient. Medications that have a side effect of reducing salivary flow were taken by 10 (33%) patients: antihypertensives (three patients), anxiolytics (three patients), both antihypertensives and anxiolytics (one patient), and nonsteroidal anti-inflammatory drugs (three patients). The stimulated salivary flow was  $0.49 \pm 0.20$  ml/min. (0.06–0.70 ml/min.).

All participants in the study maintained oral hygiene using a toothbrush and toothpaste. The majority of participants brushed their teeth two (43%) or 2–3 (29%) times a day. Twenty-one (70%) patients did not know precisely what kind of toothbrush they had, and 24 (80%) did not use dental floss. Fluoridated toothpaste has been used by 24 (80%) of participants. However, 26 (86%) have never been recommended additional use of mouth rinse with fluoride. Analysis of dietary habits revealed that patients often had poor eating habits. Apart from drinking water,

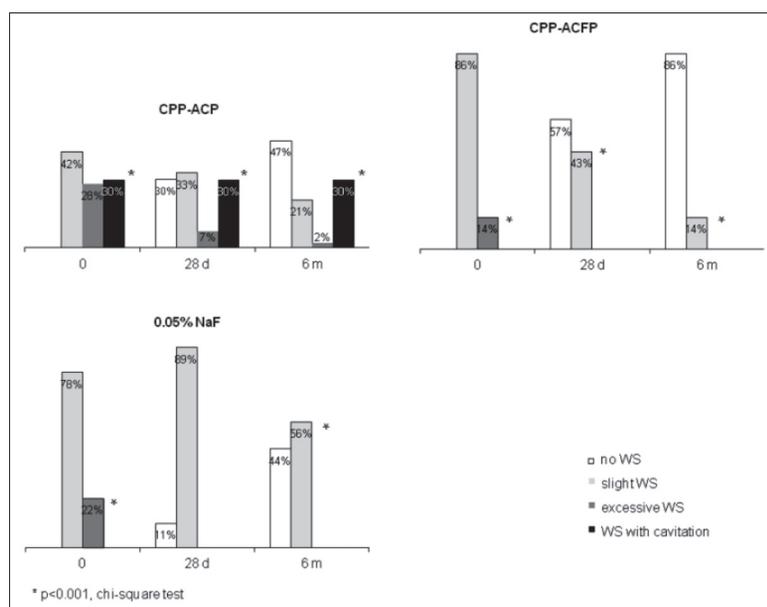
**Table 1.** Caries incidence, white spot lesion index, gingival index (GI), and oral hygiene index-simplified (OHI) values

Parameter	CPP-ACP			CPP-ACFP			0.05% NaF		
	baseline	28 d	6 m	baseline	28 d	6 m	baseline	28 d	6 m
DMFT	15 ± 6.4	15 ± 6.4	15 ± 6.4	16.8 ± 6	16.8 ± 6	16.8 ± 6	16.7 ± 11.3	16.7 ± 11.3	17 ± 11.2
CC (DFS)	20.7 ± 13.5	20.7 ± 13.5	21 ± 13.8	21.4 ± 8.6	21.4 ± 8.6	21.6 ± 8.8	14.5 ± 11.3	14.8 ± 11.7	15.2 ± 12.2
RC (DFS)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	3.8 ± 2.8	3.8 ± 2.8	3.8 ± 2.8
WSL	2.9 ± 0.9	2.4 ± 1.2	2.1 ± 1.3*	2.1 ± 0.4	1.4 ± 0.5	1.1 ± 0.4**	2.2 ± 0.4	1.9 ± 0.3	1.6 ± 0.5*
GI	0.6 ± 0.4	0.4 ± 0.2	0.5 ± 0.4	0.4 ± 0.6	0.1 ± 0.1	0.3 ± 0.5	1.4 ± 0.1	0.7 ± 0.3	0.8 ± 0.5*
OHI	0.8 ± 0.6	0.4 ± 0.3	0.4 ± 0.3	1 ± 0.7	0.6 ± 0.5	0.4 ± 0.3	1.1 ± 0.4	0.6 ± 0.4	0.3 ± 0.3*

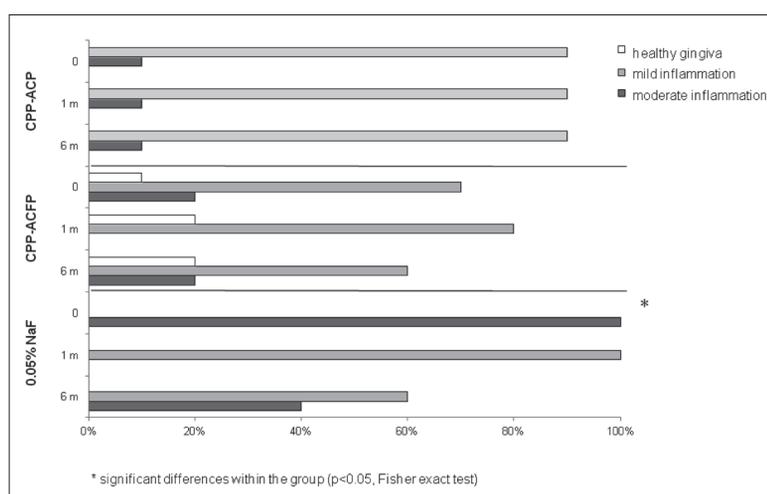
WSL – white spot lesion index; GI – gingival index; OHI – oral hygiene index-simplified; CC – coronal caries; RC – root caries; DMFT – decayed, missing, and filled teeth; DFS – decayed and filled surfaces;

\*significant difference within the group ( $p < 0.05$ , Kruskal–Wallis test);

\*\*significant difference within the group ( $p < 0.00001$ , Kruskal–Wallis test)

**Figure 1.** White spot lesion formation;

CPP-ACP – casein phosphopeptide – amorphous calcium phosphate;  
CPP-ACFP – casein phosphopeptide – amorphous calcium fluoride phosphate; WS – white spot

**Figure 2.** Gingival health

CPP-ACP – casein phosphopeptide – amorphous calcium phosphate;  
CPP-ACFP – casein phosphopeptide – amorphous calcium fluoride phosphate

the problem with dry mouth was solved by consuming sweetened beverages (57%) and confectionery products (37%).

Over an experimental period of six months, no significant changes ( $p > 0.05$ , Kruskal–Wallis test) in caries incidence were documented in the three groups (Table 1). The caries increment was the same in both the CPP-ACP and CPP-ACFP group manifesting as secondary caries on two teeth, and initial caries lesion on one tooth in the NaF group ( $p > 0.05$ , Fisher exact test). Considerable regression of WSL was noted in all three experimental groups ( $p < 0.001$ ,  $\chi^2$  test, Figure 1, Table 1). The influence of investigated agents on gingival health and oral hygiene is shown in Table 1 and Figures 2 and 3.

Three (10%) patients perceived their oral health as excellent, two (7%) described it as very good, 12 (40%) reported good oral health, while 15 (50%) patients described their oral health as being fair. Three (10%) patients believed that condition of their mouth did not affect their lives, one patient (3%) acknowledged very little influence of oral health on his life, and 12 (40%) patients reported some influence. Most of the participants in the study, 14 (47%) of them, reported a big impact of oral health on their lives.

Twenty-three (77%) patients reported that the feeling of dry mouth occurred “fairly often” or “very often.” Among other XI items, the most prominent were feeling of dry skin (83%), dry eyes (70%), dry lips (70%), and dry nose (60%). Twelve patients (40%) had problems in eating and swallowing.

The mean OHIP-14 score among SS patients was  $14.13 \pm 11.58$  (range 0–34). The prevalence of OHIP-14 individual items is shown in Table 2. During the study, no significant change in OHIP-14 score was

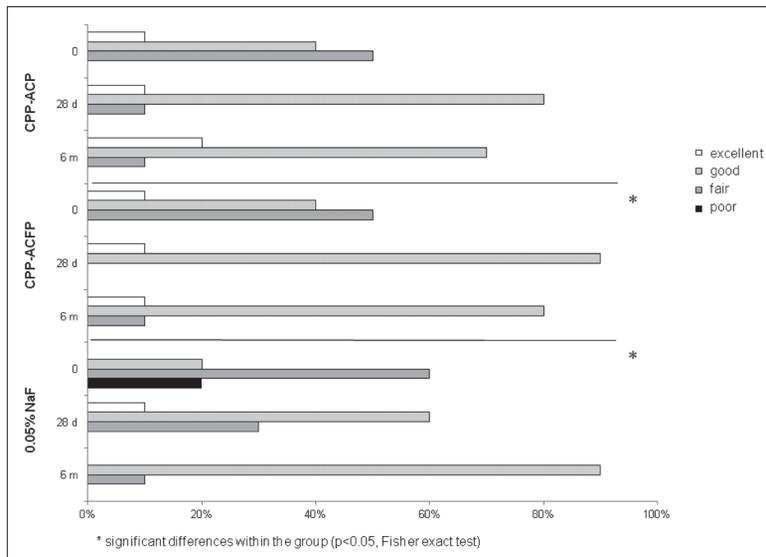


Figure 3. Oral hygiene;

CPP-ACP – casein phosphopeptide – amorphous calcium phosphate;  
 CPP-ACFP – casein phosphopeptide – amorphous calcium fluoride phosphate

Table 2. Prevalence of OHIP-14 items

OHIP-14 items	Prevalence
<b>Functional limitation</b>	
Have you had trouble pronouncing any words?	8 (27%)
Have you felt your sense of taste has worsened?	4 (13%)
<b>Physical pain</b>	
Have you had painful aching in your mouth?	10 (33%)
Have you found it uncomfortable to eat any foods?	12 (40%)
<b>Psychological discomfort</b>	
Have you been self-conscious?	3 (10%)
Have you felt tense?	2 (7%)
<b>Physical disability</b>	
Has your diet been unsatisfactory?	6 (20%)
Have you had to interrupt meals?	5 (17%)
<b>Psychological disability</b>	
Have you found it difficult to relax?	3 (10%)
Have you been a bit embarrassed?	3 (10%)
<b>Social disability</b>	
Have you been a bit irritable with other people?	3 (10%)
Have you had difficulty doing your usual jobs?	1 (3%)
<b>Handicap</b>	
Have you felt that life in general was less satisfying?	5 (17%)
Have you been totally unable to function?	0

noted in any of three experimental groups ( $p > 0.05$ , Wilcoxon test).

During the six-month observation period, reduced feeling of dry mouth was reported in CPP-ACP (scores of  $3.3 \pm 0.8$  and  $2.9 \pm 0.9$ , respectively), and CPP-ACFP group (scores of  $2.1 \pm 1$  and  $1.9 \pm 0.8$ , respectively). In addition, physical pain was reduced in all three experimental groups ( $2.2 \pm 0.4$  and  $1.8 \pm 0.5$  for CPP-ACP,  $2 \pm 1.2$  and  $1.8 \pm 1.1$  for CPP-ACFP,  $2.4 \pm 0.5$  and  $2.3 \pm 0.5$  for 0.05% NaF), but without statistically significant differences ( $p > 0.05$ , Wilcoxon test).

## DISCUSSION

Increased susceptibility to oral soft tissue diseases and caries in relation to salivary gland hypofunction has been a long-time problem for patients, as well as for dentists. Even though xerostomic patients tend to be more vigilant about their oral health, higher incidence of coronal caries, root caries, and oral soft tissue pathology comparing to healthy persons has been reported [16]. In the beginning of the present study, high prevalence of dental caries and gingivitis, poor oral hygiene and inadequate diet were found in participants. The higher risk of caries in patients with salivary gland hypofunction is due to poor self-cleaning and reduced salivary defense mechanisms. Dental plaque build-up, associated with increased concentration of pathogens, contribute to further vulnerability of dental tissues. Sometimes, mucositis and dental hypersensitivity can impede even more the maintaining of regular oral hygiene. In an attempt to stimulate salivary flow and overcome chewing and swallowing difficulties, xerostomic patients tend to excessively consume sugar-sweetened beverages and softer, more cariogenic food.

Evidence of clinical efficacy of CPP-ACP for remineralization of early caries lesion has been reported, but clinical superiority of CPP-ACP over fluoride has not been determined yet [6, 17]. In order to investigate the anticariogenic potential of calcium phosphates alone, and in comparison to an already approved remineralizing agent in patients with salivary glands hypofunction, CPP-ACP, CPP-ACFP, and 0.05% NaF have been included in the present study.

Efficacy of CPP-ACP in patients with salivary gland hypofunction has not been extensively studied. Sim et al. [18] reported lower rates of caries progression for both occlusal and smooth surfaces in persons treated with 0.4% stannous fluoride gel supplemented with CPP-ACP-containing crème. However, this study was conducted immediately after head and neck radiotherapy when none of the therapeutic agents was capable of completely preventing decay. Previously we investigated *in situ* caries-preventive potential of calcium phosphate agents in patients with SS [8]. The study revealed reduction in quantity and dimensions of enamel defects. After 28 days of CPP-ACP and CPP-ACFP application, enamel surface showed improved, more uniform and smooth appearance. The present study found no significant caries increment during the observation period. In addition, significant

WSL remineralization was noticed in the calcium phosphate groups in a short time, while the remineralization effect of NaF mouthrinse in the treatment of WSL was noticed after a six-month use.

Efficacy of prophylactic agents evaluated in the present study is probably best shown by the reduction of WSL appearance. WSL has been traditionally evaluated by direct visual examination. However, the method is not quantitative, and can be influenced by a subjective opinion of the evaluator, thus it may not be precise enough. In order to overcome these limitations, several caries quantification methods were proposed. In recent clinical studies, quantitative light-induced fluorescence (QLF) has been considered a gold standard for the detection of WSL and their longitudinal observation. The method enables monitoring and quantifying changes in the mineral content of the tooth enamel and the area of the tooth covered with WSL, but it is time consuming and not cost-effective [19]. Chairside fluorescence-based caries diagnostic methods, i.e. DIAGNOdent, proved to be less sensitive and accurate compared to QLF [20], and no better than visual diagnostics [19]. Therefore, visual evaluation of WSL, although focused only on the severity and not on the size of the lesion, is still the adequate method for everyday clinical practice.

In the present study, improved oral hygiene and subsequently better gingival status was reported in a very short time – after 28 days. Better motivation of patients and conviction that good oral hygiene habits contributed to the improvement of their general health might be the reason for such fast changes. Furthermore, changes in the DMFT/DFS distribution (higher prevalence of filled surfaces) were noted. However, patients' compliance and adherence to the oral hygiene routine tend to decrease over time. Frequent control examinations and re-motivation are of great importance in high caries risk groups. Therefore, adequate preventive, prophylactic and less invasive therapeutic procedures may retain good oral health and prevent difficult complications of salivary glands hypofunction. Another possible way to deliver oral health information to the patients might be the e-health. Today, the availability and the ease of access to the online health information have re-defined the terms of the doctor–patient relationship [21]. Although not without limitations and negative aspects, new technologies can effectively provide information, improve access to healthcare, and help patients share their experiences [22]. However, internet content is usually oriented towards dental diseases rather than prevention and oral health promotion [23]. Reliable and usable information might be of great importance, especially for patients with increased risk for oral diseases such as xerostomic patients. Patients' knowledge on oral hygiene and dietetic regimen could be improved if clinicians referred them to reliable internet educational sources. The cooperation between the specialties is mandatory, as this content should be placed on both dental and web-pages that provide information concerning systemic diseases.

Xerostomia presents an everyday challenge for persons suffering from SS. Dry mouth is usually accompanied with taste changes, burning mouth sensation, difficulties

in opening the mouth, swallowing, chewing, and speaking. Often, salivary hypofunction does not only result in uncomfortable feeling, but can seriously threaten oral and general health. The assessment of the quality of life should become an essential part of oral health evaluation. Focusing on social, emotional, and physical aspects of the illness instead of the illness *per se* may contribute to the patient motivation and active participation in the treatment and recovery [24].

In an effort to understand the efficacy of investigated agents to help SS patients overcome disability, both OHIP-14 and XI were used in the present study. Our findings confirmed that xerostomia presented significant and noticeable influence on the patients' quality of life. Almost half of the participants revealed that “fair” description of their oral status had an enormous influence on their perception of well-being and life itself. They usually complained of compromised oral functions such as talking, chewing, and swallowing, while psychological and social disabilities were rarely pointed out. Our results are in accordance with those of Locker [25], who described discomfort with eating, chewing and swallowing in elderly xerostomic patients, while prevalence of psychological and social disabilities was reported to be less than 10%. Thomson et al. [15] reported lower occurrence of functional limitations and higher rates of psychological discomfort and disability in xerostomic adults, which is in disagreement with findings of the present study. Likewise, Ikebe et al. [26] showed significant psychological and social limitations in patients with hyposalivation. The fact that the last two studies used only OHIP-14 as a survey method, may explain the differences. The OHIP-14 contains fewer questions exploring limitations of oral functions, while psychological discomfort and social disabilities are more emphasized. Therefore, more detailed questionnaire aiming to disclose relevant information regarding oral health condition and the need of dental care in persons with salivary gland hypofunction is necessary. In addition, results of the present investigation showed that CPP-ACP and CPP-ACFP agents decrease dry mouth and burning mouth sensations to some extent, which might be helpful in improving the oral discomfort in patients diagnosed with salivary gland dysfunction. Nevertheless, rehabilitation of dry mouth depends on the etiology and the treatment of systemic conditions, rather than just management of the oral symptoms. Therefore, treatment of systemic disease, i.e. adjustment to certain kind of medication, introduction to sialagogues, diet, etc., should be monitored by both the dentist and the general practitioner.

## CONCLUSION

Within the limitations of the present study, it has been demonstrated that remineralizing agents containing CPP-ACP and CPP-ACFP show promising results as caries-preventive agents for patients with SS. Even though regression of WSL was noted in three experimental groups, remineralization was faster and more pronounced in groups

treated with CPP-ACP and CPP-ACFP agents. Despite the high caries risk in SS patients, caries increment was low during the six-month observation period. Early improvement of GI and OHI suggested the importance of oral health education, frequent dental exams and motivation in patients with SS. CPP-ACP and CPP-ACFP agents might be helpful in improving the oral discomfort in patients diagnosed with salivary gland dysfunction.

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## Клиничка ефикасност казеинског фосфопептида – аморфног калцијум-фосфата и казеинског фосфопептида – аморфног калцијум-флуорофосфата и њихов утицај на квалитет живота оболелих од Шегреновог (*Sjögren*) синдрома

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### САЖЕТАК

**Увод/Циљ** Циљ рада је био да се упореди клиничка ефикасност казеинског фосфопептида – аморфног калцијум-фосфата (*CPP-ACP*) и казеинског фосфопептида – аморфног калцијум-флуорофосфата (*CPP-ACFP*) са 0,05% *NaF* и да се испита њихов утицај на квалитет живота код оболелих од Шегреновог (*Sjögren*) синдрома.

**Методе** Тридесет болесника је рандомизовано у три групе које су користиле различита средства за реминерализацију глеђи: *CPP-ACP*, *CPP-ACFP* и 0,05% *NaF*. Орално здравље је анализирано на почетку истраживања, после 28 дана (краткотрајни ефекат испитиваних средстава) и после шест месеци, и то: заступљеност обољења зуба (КЕП/кеп индекс), деминерализација глеђи (Горликов индекс беле мрље), стање гингиве (Лоу–Силнесов гингивални индекс) и ниво оралне хигијене (Грин–Вермилионов индекс). За процену симптома сувих уста и квалитета живота у вези са оралним

здрављем коришћени су упитници *Xerostomia Inventory* и *Oral Health Impact Profile*.

**Резултати** У току истраживања, прираштај каријеса ни у једној од испитиваних група није био значајан. Израженост почетних каријесних лезија значајно је редукована ( $p < 0,001$ ). Испитивана хемиопротективна средства нису значајно утицала на побољшање нивоа оралне хигијене и здравља гингиве. Примена *CPP-ACP* и *CPP-ACFP* допринела је слабијој изражености осећаја сувих уста, као и смањеном осећају печења и жарења.

**Закључак** *CPP-ACP* и *CPP-ACFP* могу допринети заустављању акутног тока каријеса и смањеној изражености симптома сувих уста код оболелих од Шегреновог синдрома.

**Кључне речи:** каријес; казеински фосфопептид – аморфни калцијум-фосфат; казеински фосфопептид – аморфни калцијум-флуорофосфат; ксеростомија; Шегренов (*Sjögren*) синдром