DOI: 10.7860/JCDR/2023/62007.17411

Review Article

Dentistry Section

Potential Effect of Casein Phosphopeptide-Amorphous Calcium Phosphate on Salivary Properties in Patients with Xerostomia: A Narrative Review

AZIZAH ALMUTAIRI[1], MAHA ALDAWSARI[2], HAFSAH AL ALI[3], ABRAR TOUNSI[4]

ABSTRACT

Changes in the makeup of saliva and/or a reduction in saliva flow are the two main causes of dry mouth. Dental caries, oral fungal infections, difficulty speaking and chewing or swallowing, mucositis, and burning mouth syndrome are associated with xerostomia, all of which have a detrimental effect on the quality of life associated with oral health. Although xerostomia is common in the general population, there are no standardised treatment standards. Recent research has indicated that topical treatments available without a prescription cannot be routinely recommended. Casein Phosphopeptide-Amorphous Calcium Phosphate complexes (CPP-ACP) and Casein Phosphopeptide-Amorphous Calcium Phosphate Fluoride have been shown to play a significant role in reducing dental caries, plaque, and pathological microorganisms, maintaining pH, and treating hypersensitivity. There is insufficient evidence that CPP-ACPs can induce salivation in patients with hyposalivation. This article reviews recent studies on the effect of CPP-ACPs on salivary traits and their use in treating patients with xerostomia.

Keywords: Hyposalivation, Mouth dryness, Saliva, Tooth mousse

INTRODUCTION

Xerostomia, or dry mouth, occurs because of alterations in the composition of saliva or decreased salivary flow [1]. The aetiology appears to be multifactorial, with the use of certain drugs, neck and head radiation, and systemic disorders (such as Sjögren's syndrome) being the most frequently reported causes [1,2]. Xerostomia is associated with dental caries, oral fungal infections, difficulty in speaking and chewing or swallowing, mucositis, and burning mouth syndrome, all of which have a negative impact on oral health-related quality of life [1,2].

Xerostomia affects between 1-29% of the population, predominantly women [3]. Multiple health issues have been demonstrated to be associated with xerostomia. Moreover, it is prevalent in older patients, individuals using specific drugs, those undergoing head and neck radiotherapy, and those with autoimmune disorders [3].

Self-reported xerostomia is significantly associated with the prevalence of diabetes mellitus (DM). Studies have reported the prevalence of xerostomia to be 3.59 times higher in individuals with DM [3]. Based on a survey conducted in the southern region of the Brazilian state of Ceará, it is the most frequent oral pathological disease among patients with cancer, with an estimated frequency of 77.3% [4].

Drugs may have a direct impact on the oral mucosa through blood circulation, or indirectly through the production of chemotherapeutic agents by saliva [4]. The decrease in mitotic potential of the oral mucosal epithelium appears to be directly related to the actions of medications [4]. In this regard, atrophy and/or ulceration of the oral mucosa followed by inflammation may be caused by a reduction in cell renewal in the basal layer of the epithelium [4].

Despite the high prevalence of xerostomia in the general population, there are currently no established treatment standards. Recent evidence indicates that non prescription topical treatments cannot be routinely recommended [1,2]. Management approaches are alleviation-oriented, ranging from the removal or reduction of the dose of xerostomic agents to lifestyle changes that include quitting smoking. Moreover, sialagogue medications such as pilocarpine and cevimeline have been demonstrated to alleviate dry mouth symptoms and increase salivary flow. Nevertheless, some patients may choose a multimodal approach of these drugs with topical therapy [1,2].

Casein phosphopeptide-amorphous calcium phosphate complexes (CPP-ACP) and casein phosphopeptide amorphous calcium phosphate fluoride (CPP-ACPF) are milk products that are utilised in dental filling materials, as well as a variety of teeth products in different presentations, such as topical pastes, gels, varnishes, and xylitol- or sorbitol-based chewing gums. It has been proven to aid in remineralisation and prevent dental caries [5]. Additionally, recent studies have reported changes in salivary properties after using CPP-ACPs. Therefore, it might be essential in the treatment of patients with hyposalivation [6,7].

The CPPs are multi-phosphorylated peptides generated from the enzymatic breakdown of casein proteins in cow milk. CPP stabilises calcium and phosphate ions in solution as ACP via phosphoseryl residues. CPPs can bind as many as 25 calcium ions, 15 phosphate ions, and five fluoride ions per molecule [8]. Casein phosphopeptides form nanoclusters with amorphous calcium phosphate, generating a calcium and phosphate pool that can maintain the supersaturation of saliva. Since CPP-ACP may stabilise calcium and phosphate in the solution, it can also aid in the pH buffering of plaque, increasing the calcium and phosphate levels in the plaque. As a result, calcium and phosphate concentrations in subsurface lesions are maintained at high levels, resulting in remineralisation [9].

Consequently, this review article aims to examine new research on the effects of CPP-ACP on salivary properties and its function in managing patients with xerostomia.

EFFECTS OF CPP-ACP ON SALIVARY PROPERTIES

Most studies on CPP-ACP have focused on its remineralisation capabilities and caries prevention [5,10-12]; however, there have been recent studies on its effect on salivary properties [6,7,9,13-16].

Salivary Flow

The average unstimulated salivary flow rate is approximately 0.3-0.4 mL/min, whereas the stimulated salivary flow rate is between 1.5-2.0 mL/min. A diagnosis of xerostomia is made when the unstimulated and stimulated salivary flow rates are ≤0.1 mL/min and ≤0.5-0.7 mL/min, respectively. Xerostomia is diagnosed in patients with apparent hyposalivation when the rate of saliva flow is less than the rate of oral mucosal fluid absorption plus the rate of oral mucosal fluid evaporation [17].

Multiple randomised controlled trials have evaluated salivary flow and capacity after using CPP-ACP gums and other types of gums, without CPP-ACP [6,7,14]. Pereira JV et al., evaluated salivary flow in a cross-sectional study on a sample of healthy young adults to assess three types of chewing gums: flavoured chewing gum without sucrose which contains CPP-ACP, another flavoured chewing gum without sucrose, and paraffin gum without flavour as a control [14]. A significant difference in the total stimulated salivary flow rate of 0.53 mL/min was noted after using flavoured CPP-ACP gums compared with paraffin gums. In contrast, no significant difference was noted in salivary flow between flavoured CPP-ACP gums and other flavoured gums [9], suggesting that the increase in salivary flow induced by mechanical stimulation could be improved by adding flavours that stimulate chemoreceptors [14].

Multiple studies have demonstrated that the taste of the gum can also affect the salivary flow rate [6,7]. Hegde RJ and Thakkar JB [6] compared salivary flow in healthy school children after using CPP-ACP-containing chewing gum and xylitol-containing chewing gum with the same flavour. Samples were collected by expectorating saliva in a preweighed graduated container using the drooling technique for five minutes. A significant rise in mean salivary flow rate was observed from baseline to immediately after spitting the chewing gum, as measured from a baseline of 0.56 mL/min to 0.91±0.34 mL/min after using CPP-ACP chewing gum, and from 0.67 mL/min to 0.87±0.31 mL/min after using xylitol-containing chewing gum. The difference in salivary flow rates between the two types of gums was not statistically significant [6].

Subsequently, Prathima GS et al., reported a similar finding in a study of children with mild molar-incisor hypomineralisation (MIH). This approach was comparable to that of Hegde RJ and Thakkar JB [6], except that the passive drooling technique was used for collection. This difference in the technique used could explain the more significant difference in results (from a baseline of 1.6±0.6 to 7.9±0.85 immediately after spitting CPP-ACP gums, and from 1.4±0.5 to 7.5±0.5 after spitting xylitol-containing chewing gums) [7]. Prathima GS et al., concluded that chewing is more important for boosting saliva production. Chewing by itself can stimulate salivary flow regardless of the type of gum used [7].

Instead of CPP-ACP chewing gums, Sim C et al., evaluated the effect of CPP-ACP paste on the salivary flow of patients with head and neck cancer undergoing radiotherapy. All patients in the trial underwent SnF2/NaF therapy and were randomly assigned to receive either a 10% CPP-ACP paste or a placebo paste with the same ingredients as the CPP-ACP paste applied three times daily. The results revealed that by 12 weeks following radiotherapy, the saliva flow was only 20% of the baseline level, and unlike CPP-ACP gums, CPP-ACP paste did not demonstrate a significant difference in stimulating salivary flow [16].

Saliva Acidity and Buffering

CPP-ACP can alkalinise plaque biofilms and possibly avert harmful microbial ecological shifts [18]. The normal pH range of saliva is 6.2-7.6, with 6.7 being the average pH. The resting pH of the mouth does not fall below 6.3 [19]. In the oral cavity, the pH is maintained near neutrality (6.7-7.3) by saliva [19].

Multiple studies have examined the effect of CPP-ACP on salivary pH [6,7,13-15,20]. Using a calibrated digital pH meter, Hegde RJ and Thakkar JB examined the effect of CPP-ACP chewing gum on the salivary pH of children in comparison to xylitol-containing chewing gum. Maximum peak rise in salivary pH was observed immediately after spitting the gum by an increase of 0.62±0.32 and 0.54±0.28 for CPP-ACP and xylitol-containing gums, respectively. Intergroup comparison of salivary pH indicated no significant differences in the stimulated saliva samples at several intervals. Meanwhile, the mean salivary buffer capacity of stimulated saliva samples increased significantly after chewing CPP-ACP gums (from 3.09 to 4.7±0.6) compared to xylitol gums (from 3.16 to 4.15±0.57). Therefore, the authors suggested that this significant increase in the buffer capacity was due to CPP-ACP acting as a calcium phosphate reservoir by causing a 5-fold increase in calcium and phosphate levels in plaque [6].

The results of the study on children with MIH conducted by Prathima GS et al., were comparable to the previous results on salivary pH alterations, whereas the difference in buffering capacity between CPP-ACP and xylitol gums was claimed to be insignificant. The authors implied that the immediate increase in salivary pH was due to the increased bicarbonate concentration in the saliva, which was proportional to the salivary flow rate. This is because chewing gum for a long time increases the stimulated saliva, leading to an elevation in pH irrespective of the type of chewing gum [7].

Padminee K et al., compared the effects of CPP-ACP and xylitol-containing gums on salivary pH in 20 healthy individuals aged 18-25 years. Although a significant improvement in salivary pH and buffer capacity compared to baseline in both the xylitol and CPP-ACP groups was observed, the baseline salivary pH comparisons between the xylitol and CPP-ACP groups were not significant. A comparison of pH showed that CPP-ACP buffered salivary pH better than xylitol after three uses in 24 h for 14 days [13]. It is worth noting that these results are most likely because a single CPP-ACP gum may contain mineral ions that are nearly as high as those seen in normal saliva or remineralising solutions. Therefore, any drop in pH could be countered by increased ion availability. Additionally, the neutral $CaHPO_4$ created by the pairing of the ions released by CPP-ACP is attributed to the absorption of most of the acid produced by the cariogenic bacteria [13].

Pereira JV et al., measured the difference in salivary flow rate among flavoured CPP-ACP gums, other flavoured gums that provide chemi-mechanical stimuli, and unflavoured paraffin gums that convey mechanical stimuli only as a control group. Differences in pH and buffering capacity were also measured in a sample of healthy young adults using a digital potentiometer. There was no significant difference between the gums, demonstrating that the flavoured CPP-ACP gums did not improve the saliva buffer capacity compared to other products used, even when compared to the unflavoured paraffin gums [14]. Methodological limitations can possibly explain these findings because only pH was measured, and salivary stimulation has the potential to promote an increase in bicarbonate concentration and, therefore, increase the buffering capacity. Thus, the values obtained from the control may be justified [14].

A study by Peric T et al., investigated the efficacy of CPP-ACP and CPP-ACPF pastes in patients with Sjögren's syndrome compared to 0.05% NaF paste. No significant alterations in salivary pH or buffering capacity were observed after the use of any of the pastes. However, there have been notable effects of CPP-ACP and CPP-ACPF on plaque pH. About 40% of patients had plaque pH below 5.5 at baseline, whereas by the end of the 28-day trial period, no pH drop below the 'critical' value was observed [15].

According to a clinical trial comparing pH level changes after the application of fluoride and CPP-ACP varnish on children's saliva, CPP-ACP and fluoride varnish significantly raised the individuals' saliva pH by 0.14 and 0.13, respectively. However, there was no significant difference between fluoride and CPP-ACP varnish in terms

of altering salivary pH [20]. The participants in the previous study received CPP-ACP (MI varnish, manufactured by GC Corporation, Japan), which contains a higher concentration of fluoride, which might explain the elevation in the salivary pH level using the varnish, whereas studies that used the paste form, which contains lower concentrations of fluoride, did not report a significant difference.

CPP-ACP in the Management of Xerostomia

Although the ability of CPP-ACP to stimulate saliva in individuals with decreased salivary flow has not been demonstrated, it has been shown to have anti-cariogenic, remineralisation, and plaque prevention properties. Since individuals with xerostomia are more likely to have erosions, caries, and tooth sensitivity, using CPP-ACP in their treatment would still be beneficial [1-3].

The CPP-ACP may positively affect the treatment and management of teeth hypersensitivity, which may play a role in the management of patients with xerostomia, as these patients frequently have tooth hypersensitivity [21]. The efficacy of CPP-ACP in treating hypersensitivity was studied by comparing CPP-ACPF, sodium fluoride, and propolis desensitising treatments administered to healthy individuals and evaluated after 60 days. The results demonstrated that each product was highly effective. Although CPP-ACPF was demonstrated to be the least effective desensitiser, the efficacy of all other desensitisers was equivalent [21]. Children with hypomineralised molars and incisors were evaluated for tooth sensitivity before and 120 days after using tooth mousse containing CPP-ACP versus a fluoride toothpaste. CPP-ACP showed a substantial reduction in thermal sensitivity from 2.4±0.6 to 1.1±0.4 and mechanical sensitivity from 7.8±1 to 3.8±0.6. In contrast, the fluoride toothpaste group showed a significant decrease in thermal sensitivity from 2.3±0.5 to 2.2±0.4, whereas the decrease in mechanical sensitivity was not significant [22].

The suggestion of whether CPP-ACP could demonstrate changes in oral health status was addressed by Sbaraini A et al., in a qualitative study in which regular users of Tooth Mousse Plus® (TMP) with incorporated fluoride (CPP-ACPF) were interviewed to assess their experiences of oral health status changes before, during, and after using TMP. Some participants had dry mouth and expressed their experience before TMP as having weak teeth, which were fragile, painful, and/or sensitive. Participants visited a dental practice once or twice a year; each time, they anticipated a need for restorative treatment. On the other hand, after regularly utilising TMP, they realised how drastically different their lives were after switching from their previous way of living. Participants valued having healthy, strong teeth that did not need to be restored frequently, seeing tangible benefits, and having pain-free teeth; however, the study was supported by the manufacturer of TMP, which could have potentially influenced the participants' responses [23].

The influence of tooth mousse and MI paste plus (CPP-ACP) and (CPP-ACPF) on patients' quality of life with Sjögren's syndrome was evaluated in an investigational study [24] comparing them to 0.05% NaF remineralising agent for a duration of six months. These findings confirmed that xerostomia had a significant and noticeable influence on patients' quality of life. Nearly half of the participants scored their oral status as 'fair', and it had a considerable impact on their well-being and their self-perception of life. During the six-month observation period, subjective feeling of dry mouth was reduced in participants using CPP-ACP (scores of 3.3±0.8 and 2.9±0.9, respectively) and CPP-ACPF (scores of 2.1±1 and 1.9±0.8, respectively), while physical pain was decreased with the use of all the three remineralising agents but without significant differences. Therefore, regardless of the type of prophylactic agent, it is possible to maintain good oral health and avoid challenging sequelae of salivary gland hypofunction by maintaining good oral hygiene and obtaining the necessary preventive treatments [24].

Banava S et al., evaluated the clinical effects of CPP-ACPF paste on the oral and salivary statuses of patients undergoing chemotherapy [25]. The patients' baseline oral health issues included mucositis, dry mouth, infection, reduced taste perception, trouble swallowing, and mucosal burning. There was no appreciable difference between patients who followed the standard preventive protocol alone and those who used CPP-ACPF paste in addition to the treatment centre's preventive protocol, even though their oral conditions, including burning sensation, were improved. No discernible difference between the patient and control groups regarding oral complications such as mucositis was found owing to the study's limitations and the small sample size [25].

Indeed, CPP-ACP is safe and well-tolerated, with no significant side-effects reported in clinical trials. CPP-ACP works by releasing calcium and phosphate ions in the mouth, which can help in strengthening the enamel of the teeth and promote remineralisation [5]. This is especially important for people with a high risk of tooth decay, such as those with dry mouth or those who consume sugary or acidic foods and drinks more frequently [1].

The strength of this report is the use of numerous recent studies conducted on CPP-ACP, which allows for a comprehensive review of the available evidence. However, only a few longitudintal studies were available to add in the present review, and the studies on CPP-ACP have used various study designs, including randomised controlled trials, observational studies, and in-vitro studies. The inclusion of various study designs made it difficult to compare the results and draw conclusions. Therefore, well designed trials with an increased number of subjects and longitudinal studies are recommended to provide evidence regarding the effect of CPP-ACP on oral health of patients with xerostomia and on other physiochemical properties of saliva such as viscosity.

CONCLUSION(S)

There is a lack of evidence that CPP-ACP can stimulate saliva in patients with hyposalivation, except in the sugar-free chewing gum form. However, chewing gum with or without CPP-ACP can stimulate saliva. The changes in salivary properties associated with CPP-ACP pastes are comparable to those associated with fluoride pastes. Patients with diminished salivary flow are at a higher risk of developing caries, tooth sensitivity, and erosion. It was proven that CPP-ACP has anti-cariogenic, remineralisation abilities and prevents plaque accumulation, which would justify its inclusion in the management of these patients. Lastly, rather than relying solely on the management of oral symptoms, management of dry mouth depends on the aetiology and treatment of underlying systemic health problems. Therefore, dentists and general practitioners should be involved collaboratively in the management of patients with xerostomia that may include therapeutic and nutritional modifications.

Acknowledgement

We wish to show our appreciation to Dr. Alhanouf Alhabdan for her valuable contribution in reviewing our work.

REFERENCES

[1] Kapourani A, Kontogiannopoulos KN, Manioudaki AE, Poulopoulos AK, Tsalikis L, Assimopoulou AN, et al. A review on xerostomia and its various management strategies: The role of advanced polymeric materials in the treatment approaches. Polymers. 2022;14(5):850.
[2] Donaldson M, Goodchild JH. A systematic approach to xerostomia diagnosis and management. Compend Contin Educ Dent. 2018;39(suppl 5):01-09; quiz 10.
[3] Fornari CB, Bergonci D, Stein CB, Agostini BA, Rigo L. Prevalence of xerostomia and its association with systemic diseases and medications in the elderly: A cross-sectional study. Sao Paulo Med J. 2021;139(4):380-87.
[4] de Araujo TLC, Mesquita LKM, Vitorino RM, de Macedo AKMN, do Amaral RC, Silva TF. Oral manifestations in patients undergoing chemotherapy. Rev Cubana Estomatol. 2015;52(4):16-21.
[5] Indrapriyadharshini K, Kumar PM, Sharma K, Iyer K. Remineralizing potential of CPP-ACP in white spot lesions-A systematic review. Indian J Dent Res. 2018;29(4):487.

[6] Hegde RJ, Thakkar JB. Comparative evaluation of the effects of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and xylitol-containing chewing gum on salivary flow rate, pH and buffering capacity in children: An in vivo study. J Indian Soc Pedod Prev Dent. 2017;35(4):332.
[7] Prathima GS, Narmatha M, Selvabalaji A, Adimoulame S, Ezhumalai G. Effects of xylitol and CPP-ACP chewing gum on salivary properties of children with molar incisor hypomineralization. Int J Clin Pediatr. 2021;14(3):412.
[8] Walsh LJ. Evidence that demands a verdict: Latest developments in remineralization therapies. Aust Dent Prac. 2009:48-59.
[9] Bullappa D, Puranik MP, Uma S. Casein phosphopeptide-amorphous calcium phosphate: A review. Int J Dent Health Sci. 2015;2:116-25.
[10] Ekambaram M, Mohd Said S, Yiu CK. A review of enamel remineralisation potential of calcium-and phosphate-based remineralisation systems. Oral Health Prev Dent. 2017;15(5):415-20.
[11] Gupta N, Nagpal R, Dhingra C. A review of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and enamel remineralization. Compend Contin Educ Dent. 2016;37(1):36-39; quiz 40.
[12] Raphael S, Blinkhorn A. Is there a place for Tooth Mousse® in the prevention and treatment of early dental caries? A systematic review. BMC Oral Health. 2015;15(1):01-12.
[13] Padminee K, Poorni S, Diana D, Duraivel D, Srinivasan MR. Effectiveness of casein phosphopeptide-amorphous calcium phosphate and xylitol chewing gums on salivary pH, buffer capacity, and Streptococcus mutans levels: An interventional study. Indian J Dent Res. 2018;29(5):616.
[14] Pereira JV, Maciel RP, Monteiro MJF, de Oliveira Conde NC, Vieira JMR, Rebelo MAB. Effect of chewing gum containing CPP-ACP on salivary flow and buffer capacity: An in vivo study. Pesqui Bras Odontopediatria Clin Integr. 2016;16(1):425-31.
[15] Peric T, Markovic D, Petrovic B, Radojevic V, Todorovic T, Radicevic BA, et al. Efficacy of pastes containing CPP-ACP and CPP-ACFP in patients with Sjögren's syndrome. Clin Oral Investig. 2015;19(9):2153-65.
[16] Sim C, Walker G, Manton D, Soong Y, Wee J, Adams G, et al. Anticariogenic efficacy of a saliva biomimetic in head-and-neck cancer patients undergoing radiotherapy. Aust Dent J. 2019;64(1):47-54.
[17] Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. Ther Clin Risk Manag. 2015;11:45.
[18] Philip N, Walsh L. The potential ecological effects of casein phosphopeptide-amorphous calcium phosphate in dental caries prevention. Aust Dent J. 2019;64(1):66-71.
[19] Baliga S, Muglikar S, Kale R. Salivary pH: A diagnostic biomarker. J Indian Soc Periodontol. 2013;17(4):461.
[20] Apriani A, Widyarman AS, Budiyanti EA, Roeslan BO. Caries activity and pH level changes after fluoride varnish and casein phosphopeptides-amorphous calcium phosphate application on children's saliva. Contemp Clin Dent. 2020;11(2):126.
[21] Pundir P, Sharma AK, Bhutia KS, Rishikesh U. Assessment of efficacy of CPP-ACP F, sodium fluoride, propolis, and placebo in treating patients with dentinal hypersensitivity. J Adv Med Dent Scie Res. 2020;8(5):151-54.
[22] Pasini M, Giuca MR, Scatena M, Gatto R, Caruso S. Molar incisor hypomineralization treatment with casein phosphopeptide and amorphous calcium phosphate in children. Minerva Stomatol. 2017;67(1):20-25.
[23] Sbaraini A, Adams GG, Reynolds EC. Experiences of oral health: Before, during and after becoming a regular user of GC Tooth Mousse Plus®. BMC Oral Health. 2021;21(1):01-17.
[24] Perić T, Marković D, Tomić-Spirić V, Petrović B, Perić-Popadić A, Marković E. 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. Srp Arh Celok Lek. 2020;148(9-10):528-34.
[25] Banava S, Houshyari M, Safaie T. The effect of casein phosphopeptide amorphous calcium phosphate fluoride paste (CPP-ACPF) on oral and salivary conditions of patients undergoing chemotherapy: A randomized controlled clinical trial. Electron Physician. 2015;7(7):1535-41.

PARTICULARS OF CONTRIBUTORS:
1. Dental Intern, College of Dentistry, King Saud University, Riyadh, Saudi Arabia.
2. Dental Intern, College of Dentistry, King Saud University, Riyadh, Saudi Arabia.
3. Dental Intern, College of Dentistry, King Saud University, Riyadh, Saudi Arabia.
4. Assistant Professor, Department of Periodontics and Community Dentistry, King Saud University, Riyadh, Saudi Arabia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Azizah Almutairi,
Dental Intern, College of Dentistry, King Saud University, Riyadh-11451, Saudi Arabia.
E-mail: azizah200000@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 07, 2022
- Manual Googling: Dec 29, 2022
- iThenticate Software: Jan 03, 2023 (13%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 02, 2022**
Date of Peer Review: **Dec 21, 2022**
Date of Acceptance: **Jan 04, 2023**
Date of Publishing: **Feb 01, 2023**