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Research progress of CPP-ACP promoting enamel remineralization

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Abstract: *With the improvement of people's living standards and the strengthening of awareness of caries prevention and control, enamel remineralization has received extensive attention. Fluoride is a commonly used remineralization agent in clinic and life, but its remineralization process depends on calcium and phosphorus ions in saliva. Therefore, several new remineralizers have been introduced to supplement and improve the repair ability of fluoride to dental minerals, such as bioactive glass, nano hydroxyapatite, casein phosphopeptide amorphous calcium phosphate (CPP-ACP), which can promote enamel remineralization to a certain extent. Casein phosphopeptide amorphous calcium phosphate (CPP-ACP), derived from milk, is a stable calcium phosphorus remineralization system, which can be used in the minimally invasive treatment of early enamel caries, and has attracted much attention in recent years. In this paper, the structure of CPP-ACP, the mechanism of remineralization and related research progress are systematically reviewed and summarized, so as to provide reference for basic research and clinical application.*

Keywords: *CPP-ACP. Caries, enamel demineralization, white spot lesions, Remineralization*

1. Introduction

As a major global public health problem, the incidence rate of dental caries in developing countries is rising. The formation process of dental caries is an unbalanced cycle between demineralization and remineralization caused by acid producing bacteria in the microenvironment [1]. White spot lesions (WSL) are characterized by demineralization of the original enamel surface and sub surface, without cavities, and are usually caused by poor oral health maintenance and plaque accumulation [2]. The clinical characteristics of wsls are usually chalky opaque appearance of dents, cracks or smooth surfaces. With the progress of demineralization, the complete tooth surface will eventually collapse and cavity [3]. Enamel remineralization is an important restoration process of dental caries [4]. In recent years, with the deepening of caries research, the most effective treatment time is in the demineralization stage. In the past decade, the focus of caries research has shifted to the development of methods to detect early caries lesions and the non-invasive management of caries lesions that protect tooth structures through remineralization [5]. Casein phosphopeptide amorphous calcium phosphate (CPP-ACP) is a new bioactive substance derived from milk protein casein. It can be used as a repository of bioavailable calcium and phosphate, promote their precipitation on the surface of enamel, and effectively enhance remineralization. In recent years, many studies have applied CPP-ACP to the treatment of demineralized enamel, early enamel caries and orthodontic leukoplakia, and achieved good results. In addition, the combined application of remineralization agents is a new research direction. The most commonly used CPP-ACP, such as the combination of CPP-ACP and fluorine, can improve the ability of enamel remineralization [6]. In this paper, the research progress of CPP-ACP promoting enamel remineralization in recent years is reviewed.

2. Structure and composition of CPP-ACP

(CPP-ACP) is a bioactive agent based on dairy products, which is prepared from two parts: casein phosphopeptide (CPP) and amorphous calcium phosphate (ACP). CPP is made of milk protein casein and has a significant ability to stabilize calcium phosphate in solution and significantly increase the level

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of calcium phosphate in dental plaque [7]. The basic structure of CPP-ACP is -serp glu-, the primary structure contains one or more SERPs, and the tertiary structure has high mobility and plasticity. SERP has a high negative charge, which can fix exogenous and endogenous calcium and phosphorus. Its structural characteristics determine that it has caries prevention and remineralization effects. Reynolds et al. [8] also confirmed this feature. In the mid-1960s, aaronsposner first described ACP. It is an initial solid phase precipitated from a highly supersaturated calcium phosphate solution, which can be easily transformed into a stable crystalline phase, such as octacalcium phosphate or apatite products [9].

3. CPP - ACP caries resistance research

3.1. CPP - ACP and mineralization mechanism research.

CPP-ACP is a remineralization technology based on dairy protective factors. CPP released from bovine cheese protein by trypsin contains a supersaturated solution of the sequence -Ser(P)-Ser(P)-Glu-Glu-Glu-stable calcium and phosphate ions to produce CPP amorphous calcium phosphate nanocomposite (CPP-ACP) [10]. Through this mechanism, CPP has a significant ability to stabilize calcium and phosphorus ions in solution and acts as a delivery carrier to significantly increase calcium and phosphorus levels in plaque. This greater potential for remineralization translates into improved clinical efficacy in preventing and reversing early caries and erosion [11]. CPP-ACP buffers free calcium and phosphate ion activity, thereby helping to maintain the supersaturated state of tooth enamel, reduce demineralization and promote remineralization. Free calcium and phosphate ions are removed from CPP, enter the enamel and reformed onto apatite crystals, inhibiting demineration and enhancing remineralization. CPP-ACP can be used to treat white spot lesions, low mineralized enamel, tooth sensitivity and erosion, and to prevent plaque buildup around alveoli and other orthodontic appliances [12]. Laboratory, animal, and human studies have also shown that CPP-ACP inhibits carious activity. Reynolds et al. [8] studies found that although CPP is eventually digested by caries-causing hydrolase in the plaque, the fixation effect of serp- on calcium and phosphorus in its structure still exists, which can confirm that the anti-caries of CPP lies in the serp- not only fixes calcium and phosphorus to the plaque and some amino acid residues near it affect the adhesion ability of polypeptides to plaque, thereby enhancing the anti-caries ability.

3.1.1. CPP-ACP combined with fluoride is used in enamel remineralization related studies

CPP-ACP in combination with fluoride forms a casein phosphopeptide-amorphic calcium fluoride phosphate (CPP-ACFP) complex that facilitates the transport of fluor ions, calcium ions, and phosphate ions deep into the lesion to promote remineralization [13]. The main products developed based on the above principles are: GC Tooth Mousse (Recaldent Corporation of Japan) (containing CPP-ACP with a mass concentration of 100 g/L), GC Tooth Mousse Plus or MI Paste Plus (Recaldent Company of Japan) (containing CPP-ACP with a mass concentration of 100 g/L and 900 mg/L fluoride ions). In recent years, many teams at home and abroad have carried out research on CPP-ACP and the joint use of CPP-ACP and fluoride for enamel remineralization, and have made some progress. However, the results of the studies were reported differently and may be associated with multiple influencing factors of intervention. Llena et al. [14] found that CPP-ACFP was significantly less severe than fluorine protective paint after 12 weeks of use, suggesting that daily use of the substance could also show better results than the use of fluorine protective paint alone. It has been found that CPP-ACP binding to fluorine can slowly release fluoride ions on the surface of the lesion, and this sustained release method can avoid the accumulation of too high concentration of fluoride on the surface of the lesion and prevent excessive mineralization of the surface of the lesion. Glaze surface phosphate stone will not accumulate rapidly, calcium, phosphorus, fluorine three ions can smoothly enter the enamel surface lesion, play a role. In a study designed to study the efficacy of CPP-ACP and CPP-ACFP on the remineralization of enamel surfaces that have caused artificial caries damage, both CPP-ACP and CPP-ACFP showed remineralization, with CPP-ACFP performing better than CPP-ACP alone [15]. Scholars such as Sun Yang [16] have also shown that fluoride-containing + CPP-ACP or bioactive glass paint has a significant effect on preventing the development of root caries. As a bioactive substance, CPP-ACP has broad application prospects for enamel remineralization in combination with fluoride. However, due to the intervention of various influencing factors such as drug action time, concentration, drug dosage form, and detection methods, the exact efficacy of the two combination needs to be further studied [13].

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3.2. CPP-ACP inhibits caries-causing effects

It has been reported in the literature that CPP-ACP inhibits the adhesion and growth of caries-causing bacteria. Reynolds et al. [8] studies have confirmed that the serp- within the structure of CPP can fix calcium and phosphorus to plaques and weaken the adhesion ability of plaques, thereby enhancing anti-caries. Liu Xingrong et al. [17] found that CPP-ACP has the effect of inhibiting the growth and adhesion of Streptococcus amoecalis, and the inhibition effect is enhanced with the increase of concentration. Further studies found the effect of CPP-ACP on streptococcus proteogenes acid production, and found that with the increase of CPP-ACP concentration, the acid production of Streptococcus aerobicum decreased, confirming that CPP-ACP has an inhibitory effect on proteococcal acid production and increased with the increase of CPP-ACP concentration [18]. Li Yanping et al. [19] found that CPP-ACP has a certain inhibitory effect on fermented Lactobacillus acid production. The bacteriostatic effect of CPP-ACP mainly has the following four aspects: (1) inhibiting the adhesion of cousin streptococcus and streptococcus mutant on the acquired membrane; (2) Indirect bacteriostatic and bactericidal effects; (3) Buffer the plaque acidic environment and inhibit enamel demineration; (4) Increase the rate of enamel loss remineralization. It effectively promotes the deposition of calcium and phosphorus at the site of carious damage [20].

4. Application status of CPP-ACP

4.1. Reminalization of early enamel caries and orthodontic leukoplakia

In recent years, many scholars have devoted themselves to the early treatment of enamel caries (including deciduous teeth), casein phosphate peptide calcium phosphate paste (CPP-ACP) has received widespread attention for improving enamel anti-caries, fixed orthodontic treatment has brought good news to patients with malocclusion deformity, and chalk stains and enamel demininеation are often found on the enamel surface after dismantling the fixed orthodontic device [21]. Foreign scholars have found that CPP-ACP significantly reduces caries activity in a dose-dependent manner, because 1% CPP-ACP reduces caries on smooth surfaces by about 55% and fissure caries activity by 46%, which is similar to the effect produced by 500 ppm fluoride. Eric et al. believe that (CPP -ACP) can always maintain a supersaturated state on the surface of tooth enamel, so that a large gradient difference in calcium and phosphorus ion concentration is formed between the tooth carious surface and plaque, which continuously supplies the calcium and phosphorus ions required for tooth remineralization, and effectively promotes the remineralization of caries. Moreover, CPP-ACP solution also has the effect of a sustained release calcium reservoir, and always maintains effective free calcium and phosphorus concentrations [22, 23, 24]. Wu Tingyun et al. [25], after CPP-ACP intervention, the SMH and Ca/P values of the enamel surface showed good reminalization effect, and the remineralization effect on caries leukoplakia after orthodontic surgery was good. Zhao Yan et al. [26] micro-CT quantitatively studied the reminalization efficiency of CPP-ACP deciduous tooth deglass, CPP-ACP can improve the calcium and phosphorus mass concentration on the tooth surface, form a calcium ion library on the tooth surface to prevent the formation of insoluble calcium phosphate and slow down the diffusion of free calcium, thereby reducing enamel demineration and providing a calcium source for remineralization. Memarpour et al. conducted a study to determine the effect of toothpaste containing CPP-ACP on remineralized leukoplakia lesions. Using laser fluorescence, regression of leukoplakia lesions can be seen after application of CPP-ACP cream [27].

4.2. Oral care industry

CPP-ACP has the commercial potential as a bioprotein preparation with higher safety performance than traditional anti-caries drugs such as fluoride, and can be used as an additive to toothpaste, mouthwash or oral spray to control caries. Reynolds et al. compared the enamel reminalization capacity of mouthwashes containing CPP-ACP and fluoride with fluoride mouthwashes. They demonstrated that 0.4% CPP-ACP and 220 ppm F produce 19% remineralization of the enamel surface, and the use of CPP-ACP and fluoride toothpaste has been shown to help reduce demineration around orthodontic brackets [28]. Another study evaluating the effects of gargling with CPP-ACP with sodium fluoride and followed up for 12 months found that CPP-ACP creams were more effective at reducing the number of leukoplakia lesions [27]. Therefore, CPP-ACP can be added as a toothpaste additive to current fluoride toothpaste to enhance efficacy. Kumar et al. demonstrated that CPP-ACP creams are very effective in remineralizing initial enamel damage. Because CPP-ACP has an additive effect with fluoride, children at high risk of

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caries are recommended to use it as a self-applied topical coating after brushing their teeth with fluoride toothpaste [29]. Currently, CPP-ACP has been shown to have the advantages of inhibiting enamel deminine, anti-allergy, and non-cytotoxicity [30, 31]. At the same time, dental care is extracted from the bioactive peptide monotylin phosphate polypeptide calcium phosphorus complex (CPP-ACP), which has higher safety performance as a biological protein preparation than traditional anti-caries drugs such as fluoride. According to Mahesuti et al., dental care agents containing CPP-ACP have been shown to be effective in treating dentin hypersensitivity [32].

4.3. Food industry

Because CPP-ACP is derived from milk and is recognized as a safe food additive, these anti-caries properties make them ideal additives to help reduce the caries-inducing properties of processed foods and have a negligible effect on taste. [33] CPP-ACP has previously been shown to reduce the cariousness of sugary mint in a dose-dependent manner [34]. Not only does demineration be prevented through frequent consumption of mints, but it also promotes the remineralization of lesions of previous demineration. Studies have shown that CPP-ACP-containing sugar-free lozenges are effective in the remineralization of enamel surface lesions. After chewing gum for 3 h, CPP-ACP can be found in plaque; In a study evaluating and estimating the concentration of calcium in saliva after chewing gum containing CPP-ACP, it was found that after chewing gum containing CPP-ACP for 10 minutes, the concentration of calcium in saliva increased by 6% in saliva and the supply of calcium at relatively high concentrations in plaque eventually reached the tooth surface and was responsible for remineralizing the tooth surface and increasing caries resistance [35]. Ramalingam et al. concluded that adding CPP-ACP to sports drinks eliminates in vitro corrosion [36]. Carbonated drinks contain carbonated acids, often with the addition of organic acids (usually citric acid) to improve taste and "taste". Citrate anion chelates calcium ions, reducing the amount of free ionized calcium available on saliva and tooth enamel surfaces, thereby enhancing demineration and reducing tooth enamel hardness [37]. In a study evaluating the effects of CPP-ACP, Panich et al. demonstrated that Coca-Cola-affected teeth showed reduced enamel hardness. However, when exposed to CPP-ACP, the surface hardness of these teeth improved [38]. A study by Walker et al. [39] found that the addition of CPP-ACP enhances remineralization despite the fact that milk contains casein phosphate. A dose of 5 grams of CPP-ACP increased reminalization by 148% compared to 2 grams of CPP-ACP per liter of milk. The addition of 2% CPP-ACP to yogurt results in a significant reduction in demineration ($p<0.0001$) compared to yogurt alone. The addition of 5% CPP-ACP to yogurt can produce a remineralization effect, significantly increasing the mineral content of the lesion ($p<0.0001$). The addition of CPP-ACP resulted in a significant dose-related increase in Ca, P, and pH ($p<0.0001$); The addition of CPP-ACP to commercial yogurt exhibits dose-related protective effects, with 5% CPP-ACP reproducing existing enamel surface damage under in vitro experimental conditions.

5. Summary

In summary, for the treatment of promoting early demineration enamel remineralization, the anti-caries and inhibition of demineration to promote the remineralization potential of CPP-ACP have been proved in rat caries models, in situ human caries models, in vitro remineralization models and human trials, and the combination of CPP-ACP and fluoride helps to enhance its remineralization effect and improve the effective utilization rate of fluoride ions on the one hand, and on the other hand, it can reduce the toxic side effects of perfluoride application, which also inspires scholars to study new ideas for the study of dental enamel reminalization. In addition, CPP-ACP is a natural derivative of milk, and unlike fluoride, it can play an important role as a food additive for controlling caries and has great application prospects. In recent years, there have been many studies on CPP-ACP laboratories and animal experiments, but more in-depth clinical research is needed for future scholars, and it is expected to find more safe and efficient, simple and convenient remineralization preparations, providing more optimized clinical applications for the prevention of caries and the inhibition of enamel demineration.

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