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Review

Preventing Dental Caries with Calcium-Based Materials: A Concise Review

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Abstract: This concise review provides an update on the use of calcium-based materials for the prevention of dental caries. Some calcium-based materials promote remineralization and neutralize bacterial acids, disrupting cariogenic biofilms and inhibiting bacterial growth. Medical Subject Headings of [Dental Caries] and [Calcium] were adopted to search publications. Information related to the aim of this review was extracted and summarized. Common calcium-based materials are calcium phosphate, hydroxyapatite, calcium carbonate, calcium fluoride and casein phosphopeptide–amorphous calcium phosphate (CPP-ACP). Calcium phosphate is commonly used in toothpaste. It provides calcium and phosphate ions, enhances the incorporation of fluoride into caries lesions and increases mineral density. Hydroxyapatite is a form of calcium phosphate that is chemically similar to the mineral found in teeth. It can be applied on teeth to prevent caries. Calcium carbonate can be found in toothpastes. It neutralizes bacterial acids and acts as a calcium reservoir during remineralization. Calcium fluoride is found in dental products and promotes remineralization as a source of fluoride, which can be incorporated into tooth enamel, forming fluorapatite and increasing resistance to caries. CPP-ACP is derived from milk proteins. It contains calcium and phosphate, which help to remineralize tooth enamel. CPP-ACP inhibits cariogenic bacteria. It also interacts with bacterial biofilms and disrupts their formation. These calcium-based materials can be used to boost the preventive effect of fluorides or, alternatively, as a therapy for caries prevention.

Keywords: caries; nanoparticles; calcium; phosphate; remineralization

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1. Introduction

Dental caries is a chronic disease affecting over 2.3 billion permanent teeth and 532 million deciduous teeth worldwide, according to the Global Burden of Disease 2017 study report [1]. It is well-documented that dental caries is caused by the demineralization of hard tissues, including enamel, dentin and cementum, due to bacterial acids over time through a complex interaction between the host, fermentable carbohydrate and cariogenic bacteria [2]. Different agents have been developed to manage this common oral disease. The well-recognized foundation of dental caries prevention (primary and secondary) is fluoride-based agents, the effectiveness of which has been widely investigated and reported [3,4]. The major mechanism of fluoride is its reaction with enamel and dentine, along with calcium and phosphate, forming calcium–fluoride-like deposits during the process of remineralization [5]. Despite the well-known benefits of fluoride agents, dental researchers are exploring the use of different materials to prevent and arrest carious lesions. This may be due to the adverse effects of fluorides, like dental and skeletal fluorosis. The adverse effects also direct dental professionals to explore alternatives or boosters of fluorides for dental caries prevention [6].

Calcium-based materials have been introduced to prevent dental caries. The three types of hard tissues of the tooth, namely enamel, dentin and cementum, are mainly composed of hydroxyapatite, a mineral form of calcium. The net loss of calcium and phosphate ions from the tooth structure due to cariogenic bacteria will lead to dental caries [7]. Therefore, adding calcium and phosphate back to the tooth structure from supersaturated oral fluid and controlling bacteria activities plays an important role in dental caries prevention [8]. During the process of tooth remineralization, it is important that calcium and phosphate are abundant in the saliva. Unfortunately, however, calcium and phosphate are normally limited. Calcium-based materials refer to substances that contain calcium as a primary component or play a significant role in providing calcium ions. In the discipline of dental caries prevention, calcium-based materials are used to promote tooth remineralization and manage bacteria activity [9,10]. They can be used as adjunctive treatment with fluorides or alternative therapy for dental caries control. These materials show excellent biocompatibility, and some of them have been adopted in dental practice.

Understanding recent research advances helps clinical practitioners to incorporate the latest calcium-based materials and techniques into their practice and facilitate dental researchers in developing new formulations and improving this discipline. The aim of this narrative review is to provide an update on the use of calcium-based materials for dental caries prevention. The properties of different calcium-based materials, their ability to remineralize and manage bacterial activity and mechanisms, and their clinical applications and effectiveness are summarized herein.

2. Results

The results showed that calcium phosphate, hydroxyapatite, calcium carbonate, calcium fluoride and casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) are the commonly reported calcium-based materials in the discipline of dental caries prevention. There are also other derivates of these calcium-based materials, such as sodium–calcium phospsilicate, sodium trimetaphosphate and calcium glucerophosphate as well as calcium nanoparticles. This manuscript mainly focuses on the commonly reported calcium-based materials (Table 1). Other forms of advanced materials are introduced in the discussion.

2.1. Calcium Phosphate

Calcium phosphates usually refer to a family of materials containing calcium ions combined with phosphate anions such as phosphate, monohydrogen phosphate and dihydrogen phosphate. The most frequently used ones are tricalcium phosphate and hydroxyapatite, which contains hydroxyl anions and is discussed in the following paragraph [11]. Tricalcium phosphate is commonly used in toothpaste, dentifrice, mouthwash and chewing gum to promote the remineralization of teeth [12]. It is a white solid which can be found in bone and tooth enamel. It is soluble in acid, but it has low solubility in water. It exists as three crystalline polymorphs, namely α, α' and β. Among them, β-tricalcium phosphate is stable at room temperature and becomes the bioavailable form used in oral care products. α-Tricalcium phosphate is less soluble than β-tricalcium phosphate. It is rare as it only exists at high temperatures above 1125 °C [13]. α'-Tricalcium phosphate is less common than α-tricalcium phosphate and has limited applications.

Researchers in the early 1990s found that the combined use of calcium phosphate and fluoride accelerates the setting and hardening of the compound [14]. However, it is difficult for these two substances to coexist in an oral care product as tricalcium phosphate can interact with fluoride to form calcium fluoride and therefore lower the bioavailability of both calcium and fluoride [15]. To solve the problem, a novel functionalized tricalcium phosphate was developed by coupling β-tricalcium phosphate with organic and/or inorganic moieties [16]. It was suggested that these molecules prevent premature fluoride–calcium interactions and enhance fluoride-based nucleation activity, subsequently leading to remineralization.

The potential of functionalized tricalcium phosphate for remineralization has been reported. In a laboratory study, functionalized tricalcium phosphate paste was applied on an artificial white spot lesion and showed a significantly greater increase in mean microhardness than casein phosphopeptide–amorphous calcium phosphate fluoride and the negative control [17]. Regarding enamel carious lesions, toothpaste containing functionalized tricalcium phosphate showed no significant difference in the percentage of remineralization potential and percentage of hardness recovery when compared to fluoride toothpaste [18]. A study reported that functionalized tricalcium phosphate promoted the incorporation of fluoride into root caries lesions and increased mineral density [19]. Few studies reported the effectiveness of functionalized tricalcium phosphate on cariogenic bacteria alone, given that it could be used in combination with other antibacterial agents. An in vitro study reported that the combination use of silver nitrate solution and sodium fluoride varnish containing functionalized tricalcium phosphate reduced cariogenic biofilm [20].

The clinical effectiveness of functionalized tricalcium phosphate in preventing dental caries has also been reported. In a clinical study, fluoride varnish was applied with functionalized tricalcium phosphate on white spot lesions at baseline and at 8 weeks among patients with fixed appliances and assessed at 16 weeks. The results indicated that 62% of the white spot lesions in the test group were reversed [21]. In another clinical study, silver nitrate solution and sodium fluoride varnish with functionalized tricalcium phosphate were adopted in order to arrest dentine caries among children [22]. The results indicated that the test group with functionalized tricalcium phosphate had a higher arrest rate than that without functionalized tricalcium phosphate. These results suggest that functionalized tricalcium phosphate has promising effects in preventing dental caries, but more clinical evidence is required to confirm its clinical use.

2.2. Hydroxyapatite

Hydroxyapatite is a naturally occurring mineral form of calcium apatite. Up to 70% by weight of human bone consists of a modified form of hydroxyapatite, and hydroxyapatite is the main mineral making up dental enamel and dentin. The solubility of hydroxyapatite in human dental enamel varies linearly with acidity, from 10 to 57 at pH 4.6 to 10 to 53 at pH 7.6 [23]. Hydroxyapatite is commonly added to toothpaste, dentifrice and mouthwash for daily oral care due to its ability to remineralize and manage oral bacteria [24]. A study reported that hydroxyapatite particles in toothpaste have the ability to bind to the damaged tooth surface and restore the surface integrity, and they are also able to penetrate into the deeper layers of the carious lesion [25]. Hydroxyapatite-based gel exhibited a significantly higher percentage of mineral gain in caries-like lesions after being subjected to the pH-cycling model when compared to artificial saliva [26]. Furthermore, hydroxyapatite in mouthwash could inhibit biofilm formation by preventing bacteria from binding to the tooth surface [27]. Instead, bacteria would bind to the hydroxyapatite particles and be cleared from the oral cavity. A review summarized that hydroxyapatite could be used to control biofilm by reducing bacterial attachment to enamel surfaces without antibacterial effects [28].

Some reviews and meta-analyses on the application of hydroxyapatite and its clinical effectiveness in preventing dental caries have been published. A systematic review on hydroxyapatite-based, fluoride-free oral care products was conducted and published in 2021. The results of the meta-analysis on three randomized control trials showed that hydroxyapatite toothpaste protected enamel from dental caries [29]. Another 18-month, double-blinded clinical trial reported that fluoride-free hydroxyapatite toothpaste was not statistically inferior to a fluoride toothpaste in preventing dental caries among adults [30]. The results of these studies suggest that hydroxyapatite is effective in preventing dental caries and has the potential to be an alternative to fluoride.

2.3. Calcium Carbonate

Calcium carbonate is the major constituent of limestone, marble, chalk, eggshells, bivalve shells and corals. It has the appearance of a white powder, a colorless crystal white powder or colorless crystals. Calcium carbonate is commonly added to dentifrice or toothpaste as an abrasive that removes dental plaque, and it is also used as a white coolant or thickener. It has low solubility in water but is soluble in dilute acid. Therefore, it has acid-buffering and calcium-releasing properties, which reverse the effects of the acids produced by bacteria [31].

It has been reported that calcium carbonate helps to neutralize plaque acid, increases the calcium level in dental plaque and acts as a calcium reservoir during remineralization [32]. A study reported that calcium–carbonate-based dentifrice was able to increase surface microhardness and was more effective in enamel remineralization when compared to the negative control [33]. Toothpaste containing arginine, calcium carbonate and sodium fluoride showed better recovery in microhardness and lesion depth after remineralization cycling treatment when compared to toothpaste containing sodium fluoride solution [34]. Adopting calcium carbonate alone to manage cariogenic bacteria was seldom reported on. An in vitro study reported that desensitizing paste containing 8% arginine and calcium carbonate reduced the formation of *Streptococcus mutans* biofilm on dentine [35].

As early as the 1950s, a study reported on the role of calcium carbonate in dental caries [36]. A clinical study reported that school children treated with a dentifrice containing regular fluoride content and calcium carbonate as a polishing agent had a tendency toward fewer decayed surfaces [37]. After that, several clinical trials reported that the adoption of calcium–carbonate-based fluoride toothpaste in daily oral health practice reduced dental caries increments [38,39]. An in vivo study reported that calcium–carbonate-based toothpastes could significantly reduce plaque acidity after a cariogenic challenge when compared to those without calcium carbonate [40]. These studies confirmed the clinical effectiveness of calcium carbonate in fluoridated dentifrice/toothpaste in preventing dental caries.

2.4. Calcium Fluoride

Calcium fluoride has a great variety of applications in dental caries prophylaxis. It is a white, solid, inorganic compound that is practically insoluble in water but slightly soluble in acid. The major cariostatic mechanism of fluoride is the formation of fluorapatite or calcium–fluoride-like precipitates, which are less soluble than hydroxyapatite when attacked by acid [41]. Both calcium and fluoride ions are prerequisites for remineralization, but premature calcium–fluoride interactions remain a challenge [42].

Calcium fluoride has also been suggested to act as an acidity-dependent reservoir of fluoride that can be incorporated into the tooth enamel, forming fluorapatite and increasing resistance to acid attacks [43]. However, its dissolution has been suggested to be controlled by the presence of phosphate and acidity. In a laboratory study, calcium fluoride particles were incubated with human enamel samples to provide a constant supply of soluble fluorides in a phosphate-free buffer solution. Despite this, the solubility of these particles and the release of fluoride were reduced when incubated in human saliva [44]. Though calcium fluoride has no bactericidal effect, it can be used in combination with other agents to enhance their antimicrobial properties. A laboratory study reported that composite materials modified with calcium fluoride highly reduced growth of two common cariogenic bacteria, *Lactobacillus acidophilus* and *Streptococcus mutans* [45]. Calcium fluoride can be used to produce gels, mouthwashes and pastes that strengthen tooth enamel and protect against acids. However, few clinical studies have been conducted that report the clinical effectiveness of calcium fluoride in preventing dental caries.

2.5. Casein Phosphopeptide–Amorphous Calcium Phosphate

Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) is commercially available and biocompatible and has attracted considerable research attention in recent years. Amorphous calcium phosphate (ACP) is a glassy solid. Casein phosphopeptides (CPPs) are derived from milk and can stabilize calcium and phosphate in ACP solution. This complex delivers calcium and phosphate ions to the tooth surface [46]. CPP-ACP can also interact with fluoride ions to form casein phosphopeptide–amorphous calcium fluoride phosphate (CPP-ACFP) [47].

CPP-ACP has been shown to have high remineralization potential for white spot lesions, dentine caries and non-cavitated root decay [48–50]. An in situ study revealed that fluoride toothpaste containing CPP-ACP increased the surface hardness of the demineralized enamel slab [51]. An in vitro study indicated that applying CPP-ACP on dentine surfaces led to lower demineralization and higher remineralization when immersed in demineralization solution [49]. It was proposed that ACP is localized in dental plaque and maintains a state of supersaturation with calcium and phosphate ions, thereby depressing demineralization and enhancing remineralization [52]. However, some reviewers reported that CPP-ACP/CPP-ACFP can inhibit demineralization but is less effective when compared to fluoride agents [53]. A systematic review with meta-analysis suggested that CPP-ACP/CPP-ACFP can be an adjunct to fluorides in caries prevention but cannot be an alternative [54].

CPP-ACP can also inhibit the activity of bacteria and the formation of biofilm. It has been reported that the addition of CPP-ACP to glass ionomer cement significantly reduced the growth of *Streptococcus mutans* in a dentine caries model [55]. Another laboratory study found that CPP-ACP reduces biofilm formation of *Streptococcus mutans* but does not kill the bacteria [56]. A clinical study reported that fluoride varnish containing CPP-ACP effectively reduced the salivary *Streptococcus mutans* count among children in mixed dentition [57]. Another clinical trial revealed that 5% sodium fluoride varnish with tricalcium phosphate significantly reduced saliva *mutans streptococci* among children with severe early-childhood caries [58].

CPP-ACP can be found in toothpaste, mouthwash, chewing gum and dental cream. A systematic review on clinical studies reported that fluorides combined with CPP-ACP achieved the same efficacy as fluorides monotherapy for early caries lesions on smooth surfaces, but the combination treatment had better efficacy than fluorides monotherapy for occlusal early carious lesions [59]. A randomized clinical trial reported that participants who chewed sugar-free gum containing CPP-ACP had 18% less tooth surface progression to dental caries when compared to those who chewed gum without CPP-ACP [60]. However, a systematic review also suggested that although CPP-ACP was more effective than a placebo in managing dental caries, its effectiveness was borderline when compared with fluoride [61]. Therefore, CPP-ACP can be an additive to fluoride but not an alternative to managing dental caries.

Table 1. Properties, application and clinical findings of calcium-based materials for caries prevention.

Calcium-Based Material	Properties	Applications	Clinical Findings [Reference]
Calcium phosphate	1. Remineralization	1. Toothpaste 2. Mouthwash 3. Chewing gum	1. Reverses white spot lesions [1] 2. Arrests caries with fluoride agents [21]
Hydroxyapatite	1. Remineralization 2. Bacterial inhibition	1. Toothpaste 2. Mouthwash	1. Reduces caries incidence [27,28]
Calcium carbonate	1. Remineralization 2. Buffer effect	1. Toothpaste	1. Reduces caries incidence [34] 2. Reduces caries increments [35,36]
Calcium fluoride	1. Remineralization 2. Bacterial inhibition	1. Mouthwash 2. Gel and paste	-
Casein phosphor–peptide–amorphous calcium phosphate	1. Remineralization 2. Bacterial inhibition	1. Toothpaste 2. Mouthwash 3. Chewing gum 4. Cream	1. Prevents early caries lesions [55] 2. Reduces caries incidence [56]

3. Methods

This concise review screened publications related to calcium-based materials in the discipline of dental caries prevention. Medical Subject Headings including [Dental Caries] and [Calcium] were adopted to search publications. Information regarding the properties of different calcium-based materials, their remineralization ability and impact on cariogenic bacteria and their clinical application was extracted and summarized.

4. Discussion

Calcium-based materials have shown great potential in the treatment of dental caries. Dental caries is a common dental problem caused by the demineralization of hard tissue by acids produced by cariogenic bacteria in the mouth. Therefore, the inhibition of demineralization and cariogenic bacteria is of great importance in preventing dental caries. During the process of remineralization, lost minerals such as calcium phosphate and fluoride are restored to the hard tissues, which helps to reverse the process of dental caries at the initial stage and inhibits further progression of cavitated lesions [12]. Calcium-based materials can saturate saliva and fluid with calcium ions (sometimes along with phosphate ions), neutralize the acidic environment, exchange ions between saliva and the tooth surface and form less soluble minerals [62]. In the past, the clinical use of calcium and phosphate ions for remineralization was not successful because of the low solubility of calcium-based materials as well as their premature interaction with fluoride ions [9]. In recent years, materials such as functionalized tricalcium phosphate have been developed to maintain the active calcium and fluoride during storage. Some studies suggested that calcium–phosphate materials had the potential to act as delivery systems in the mineralized tissue engineering field. These materials carry relevant substances to drive remineralization of dentin and/or stem cell differentiation within dental pulp [63]. New synthesis techniques may help to develop preferable calcium-based materials to prevent dental caries and reduce the risk of irreversible dental pulp damage in the future.

Some calcium-based materials have an influence on cariogenic bacteria. However, it has also been suggested that calcium-based materials do not have a bactericidal effect on their own. Instead, they inhibit the growth and adherence of cariogenic bacteria to control bacterial activity. CPP-ACP has been reported to interfere with the growth and adherence of *Streptococcus mutans* and *Streptococcus sobrinus* [64]. Free hydroxyapatite particles in toothpaste and mouthwash attract microorganisms, which attach to the particles and therefore clear microorganisms from the oral cavity [27]. A few studies reported the influence of calcium-based materials on the formation of biofilm even though these materials had no bactericide effect. These materials controlled the biofilm by inhibiting the attachment of bacteria to the tooth surface without killing bacteria. They can also be used in combination with other antibacterial agents and help to improve the effectiveness of controlling cariogenic bacteria and biofilm as well as the effectiveness of the prevention of dental caries. Though these calcium-based materials are widely used in daily oral health care, more clinical evidence is needed to confirm their clinical use and effectiveness in preventing dental caries among different people.

Nanotechnology has been adopted in the development of calcium-based materials such as nanoparticles of amorphous calcium phosphate, calcium phosphate nanocomposite and nano-hydroxyapatite. It has been reported that these calcium-based materials' nanoparticles release more ions than those at the micron scale because of the high surface-area-to-volume ratio [65]. As a result, the remineralization was enhanced. For example, nano-hydroxyapatite was reported to have greater remineralization effects on demineralized bovine dentine when compared to amine fluoride toothpastes [66]. A two-year clinical trial reported that nano-hydroxyapatite gel was effective in remineralizing proximal caries [67]. Nano-sized amorphous calcium phosphate was found to release more calcium and phosphate ions at a low pH, have lower mineral loss and decrease the carious lesion depth [68]. Thus, these nano-sized materials have the potential to be used in dental caries prevention, but more clinical evidence is needed in the future.

There are other derivates of these calcium-based materials, such as sodium–calcium phosposilicate, sodium trimetaphosphate, calcium glucerophosphate, glass–ionomer cement and bioactive glass. These materials have also been adopted in different forms of oral health care products to prevent dental caries. Toothpaste containing sodium–calcium phosposilicate has been reported to have the potential to remineralize enamel [69]. Fluoride varnishes containing sodium trimetaphosphate enhanced the remineralizing effect of artificial caries lesions by increasing the percentage of surface hardness recovery [70]. A literature review concluded that calcium glycerophosphate can reduce the plaque mass and have a greater anti-caries effect than sodium monofluorophosphate [71]. Glass ionomer cements, which are commonly used as a filling material and luting cement, had the ability to remineralize carious tooth surface and exert a bacteriostatic effect [72]. A randomized clinical trial indicated that glass ionomer sealants can effectively prevent dental caries [73]. A systematic review on bioactive glass, which can be adopted as a dental restorative material and mineralizing agent, indicated its effectiveness in remineralizing and forming apatite on the tooth surface of enamel and dentine. Besides, bioactive glass has also been reported to have an antibacterial effect on cariogenic bacteria [74].

Our concise review summarizes the commonly used calcium-based materials and provides an overview of their properties as well as their role and clinical effectiveness in dental caries prevention. Nevertheless, this concise review provides an overview and not in-depth details for researchers.

5. Conclusions

Calcium-based materials such as calcium phosphate, hydroxyapatite, calcium carbonate, calcium fluoride and casein phosphopeptide–amorphous calcium phosphate can be used to boost the preventive effect of fluorides or, alternatively, as a therapy for caries prevention. Moreover, they have the potential to be used as drug delivery systems in the mineralized tissue engineering field. More clinical evidence is needed to warrant their clinical use.

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