LEARNING OBJECTIVES

- understand the process and importance of remineralization
- list the various types of remineralizing agents and their roles in the prevention of caries
- explain how caries management can be enhanced by improving the remineralization process

ABSTRACT

Minimal intervention is a key phrase in today’s dental practice. Minimal intervention dentistry (MID) focuses on the least invasive treatment options possible in order to minimize tissue loss and patient discomfort. Concentrating mainly on prevention and early intervention of caries, MID’s first basic principle is the remineralization of early carious lesions, advocating a biological or therapeutic approach rather than the traditional surgical approach for early surface lesions. One of the key elements of a biological approach is the usage and application of remineralizing agents to tooth structure (enamel and dentin lesions). These agents are part of a new era of dentistry aimed at controlling the demineralization/remineralization cycle, depending upon the microenvironment around the tooth. This article details the various agents that enhance and/or promote remineralization and discusses their clinical implications.
The oral cavity is a battlefield of activities of demineralization and remineralization (Figure 1). The ratio between demineralization and remineralization is crucial, determining the hardness and strength of tooth structure. Demineralization results from a complex chemistry between bacteria, diet, and salivary components. A drop in the pH in the oral cavity results in demineralization, and the oral environment becomes undersaturated with mineral ions, relative to a tooth’s mineral content. A drop in the pH is due to the organic acids (ie, lactic acid) that are produced by the action of plaque bacteria in the presence of dietary carbohydrates. If the demineralization phase continues for a long period of time, excessive loss of minerals results, which leads to loss of enamel structure and cavitation—the typical characteristics of dental caries. This dissolution continues until the pH returns to normal level.

When the pH rises, the reverse takes place, resulting in deposition of mineral back to the tooth structure. Thus, conversely, remineralization occurs when pH rises and there is deposition of calcium, phosphate, and fluoride ions in the form of fluorapatite, which are more resistant to crystals’ dissolution by organic acids. During remineralization, growth of newly formed crystals (fluorapatite) takes place, and, with advancing growth, the crystals fuse with each other to form large crystals with hexagonal outlines. Therefore, the best strategy for caries management is to focus on the methods of improving the remineralizing process with the aid of remineralization products. Contemporarily, a variety of remineralizing agents like fluorides, casein calcium phosphopeptides, NovaMin®, etc, that aid in remineralization of tooth structure are available commercially (Table 1 through Table 5). This article provides an overview of the various available agents and their roles in the remineralization of tooth tissue as well as their dispensing methods and clinical implications.

REMINERALIZING AGENTS

Fluorides
Fluorides are an important adjunct in the prevention of dental caries. They are introduced into the oral environment via personal (eg, dentifrices, rinses) or professional applications (eg, varnishes, foams, gels, fluoride-releasing restorative materials). Fluoride levels of about 3 parts per million (ppm) in the enamel are required to shift the balance from net demineralization to net remineralization. Several mechanisms have been suggested to achieve the anticaries effects of fluoride, including the formation of fluorapatite, which is more acid-resistant than hydroxyapatite; the enhancement of remineralization; interference of ionic bonding during pellicle and plaque formation; and the inhibition of microbial growth and metabolism. Fluoride can be used in combination with sodium, tin, or titanium. The newly introduced titanium fluoride (TiF) exhibits enhanced uptake of calcium, and TiF-pretreated enamel also shows less loss of calcium during demineralization.

Casein Phosphopeptides (CPP)
Casein phosphopeptides are the latest entry into preventive dentistry. They are used alone or as CPP-ACP (casein phosphopeptides with amorphous calcium phosphate) or CPP-ACFP (casein phosphopeptides with amorphous calcium fluoride phosphate). CPP-ACP has shown to reduce demineralization and enhance remineralization of the enamel subsurface carious lesions. The main function of casein phosphopeptides is to modulate bioavailability of calcium phosphate levels by maintaining ionic phosphate and calcium supersaturation to increase remineralization. The role of ACP is also said to control the precipitation of CPP with calcium and phosphate ions. The advantage of CPP-ACFP is the availability of calcium, phosphate, and fluoride in one product. Each molecule of CPP can bind up to 25 calcium ions, 15 phosphate ions, and 5 fluoride ions. The calcium phosphate in these complexes is biologically available for remineralization of subsurface lesions in tooth enamel.
CPP also is believed to have an antibacterial and buffering effect on plaque and interfere in the growth and adherence of *Streptococcus mutans* and *Streptococcus sobrinus*. It has been observed that CPP-ACP significantly reduced caries activity in a dose-dependent manner, as 1% CPP-ACP produced about a 55% reduction in smooth surface caries and a 46% reduction in fissure caries activity, which is similar in effect to that produced by 500 ppm of fluoride. Combined with fluoride, CPP-ACP has an additive effect on caries activity.10,12 Use of CPP-ACP along with fluoride-containing dentifrice has proved to be beneficial in reducing the demineralization around orthodontic brackets and remineralizing white spots caused by demineralization.13,14 Ramalingam et al15 found that adding CPP-ACP to soft drinks can reduce their erosion capacity. CPP-ACP has also been added to dentifrices, mouthrinses, chewing gums, lozenges, and bovine milk. A study by Walker et al16 found that although milk contains casein phosphate, addition of CPP-ACP results in enhanced remineralization. A dose of 5 gm of CPP-ACP produced 148% more remineralization compared to 2 gm of CPP-ACP per liter of milk.

Sugar Substitutes
Xylitol is a commonly used sugar substitute, especially in chewing gums. A nonfermentable sugar alcohol acts as a carrier or reservoir for calcium phosphates.17 In a trial, Manton et al18 showed that a sugar-free gum containing xylitol produces superior remineralization. The addition of fluoride to xylitol is said to provide additional benefit, assuming the fluoride concentration is more than 0.8 ppm. Xylitol restrains remineralization when the concentration of available fluoride is low.19 Besides fluoride, calcium lactate also enhances remineralization when added to xylitol.20 Sorbitol is another sugar substitute that is used as an artificial sweetener. The abilities of xylitol and sorbitol to remineralize early enamel caries seem to be almost similar.21 Isomalt is a noncariogenic sweetener that is widely used as a sugar substitute. Adding isomalt to a demineralizing solution has shown to significantly reduce tooth mineral loss.22

Calcium Sodium Phosphosilicate
NovaMin® (calcium sodium phosphosilicate) is the trademark product of NovaMin Technology Inc. (NTI), which was acquired by GlaxoSmithKline in 2009. The compound is a bioactive glass composed of minerals that naturally occur in the body and reacts when it comes into contact with water, saliva, or other body fluids. This reaction releases calcium, phosphorus, sodium, and silicon ions in a way that results in the formation of new hydroxy-carbonateapatite (HCA) crystals.23

Ozone
Ozone is a chemical compound consisting of three oxygen atoms (O₃, triatomic oxygen). Ozone therapy has proven to be effective with a wide range of dental applications, including prosthodontics, endodontics, periodontics, surgical procedures, and preventive dentistry.24 It is usually advocated in dentistry for sterilization of cavities, root canals, periodontal pockets, and herpetic lesions. Ozone therapy is also proposed to stimulate remineralization of incipient caries following treatment for a period of about 6 to 8 weeks.24,25

Hydroxyapatite
Carbonate hydroxyapatite nanocrystals, having size, morphology, chemical composition, and crystallinity comparable to that of dentin, are said to remineralize enamel.26 A concentration of 10% nanohydroxyapatite is optimal for remineralization of early enamel caries.27 Hydroxyapatite has been used in toothpastes (as fillers) and pit-and-fissure sealants. Hydroxyapatite crystals can effectively penetrate the dentin tubules and obliterate them and can cause closure of the tubular openings of the dentin with plugs within 10 minutes as well as a regeneration of a surface mineral layer.26,27

Dispensing Methods
Remineralizing agents can be incorporated into different products for application. Commonly used vehicles are restorative materials, pit-and-fissure sealants, dentifrices, chewing gums, and rinses.

Restorative Materials
Fluoride-releasing materials used in restorative dentistry are glass ionomers, compomers, and giomers.28,29

Glass Ionomers
Fluoride released from a glass-ionomer restoration has been found to be incorporated in adjacent tooth enamel and saliva.30 It has been observed that fluoride released from restorative materials has an effective zone of about 1 mm from the restoration’s margin.23 Glass ionomers also incorporate into bacteria, thus inhibiting bacterial acid production.31,32 Comparing their fluoride-releasing ability, conventional glass ionomers release comparatively large amounts of fluorides compared to resin-modified glass ionomers. Salivary fluoride concentration is found to remain elevated for up to 1 year after placement of glass-ionomer restorations (0.3 ppm after placement and 0.04 ppm 1 year later).33 Perrin et al34 reported that the greatest release of fluoride from glass ionomer...
Fluoride release capacity: fluoride-releasing resin-based composites do not release any additional fluoride after being exposed to a fluoride-rich solution. Compomers have recharge capacity intermediately between resin-modified glass ionomers and resin composites. The recharge ability of these materials may be due to the microporosity present in conventional and resin-modified glass ionomers. Topical fluorides form the main source for recharging of these restorative materials, which depends on the pH of the fluoride agent. Acidic topically fluoride solutions found in acidulated phosphate fluoride solutions and other acidified fluoride preparations cause degradation of glass-ionomer materials and should, therefore, be avoided. Resin-modified glass ionomers are more resistant to surface degradation than conventional glass ionomer but still degrade when exposed to acids.

**TABLE 2**

**Dentifrices**

<table>
<thead>
<tr>
<th>FLUORIDE:</th>
<th>MANUFACTURER</th>
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<tbody>
<tr>
<td>Lacer® (NaF)</td>
<td>Lacer, S.A. (<a href="http://www.lacer.es">www.lacer.es</a>)</td>
</tr>
<tr>
<td>Fluocaril® Bi-Fluoré 250 (NaF + NaF)</td>
<td>Procter &amp; Gamble Co. (<a href="http://www.pg.com">www.pg.com</a>)</td>
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<tr>
<td>Colgate Fluor-Active (AmF)</td>
<td>Colgate-Palmolive Co. (<a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>)</td>
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<tr>
<th>XYLITOL:</th>
<th>MANUFACTURER</th>
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<tr>
<td>Squigle® (36% xylitol with fluoride): Tooth Builder* (without fluoride)</td>
<td>Nature’s Provision (<a href="http://www.xylipro.com">www.xylipro.com</a>)</td>
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<th>NOVAMIN:</th>
<th>MANUFACTURER</th>
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<tr>
<td>Restore™</td>
<td>Dr. Collins (<a href="http://www.drcollins.com">www.drcollins.com</a>)</td>
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<tr>
<td>Oravive™ Tooth Revitalizing Paste</td>
<td>Oravive Co. (<a href="http://www.gsk.com">www.gsk.com</a>)</td>
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<td>Nupro® NuSolutions™</td>
<td>DENTSPLY (<a href="http://www.dentsply.com">www.dentsply.com</a>)</td>
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<td>SootheRx™</td>
<td>Omni Oral/3M ESPE</td>
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<td>X-Pur</td>
<td>Oral Science (<a href="http://www.x-pur.com">www.x-pur.com</a>)</td>
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<td>SHY-NM™</td>
<td>Group Pharmaceuticals Ltd. (<a href="http://www.grouppharma.in">www.grouppharma.in</a>)</td>
</tr>
<tr>
<td>Topex® ReNew™</td>
<td>Sultan Healthcare (<a href="http://www.sultanhealthcare.com">www.sultanhealthcare.com</a>)</td>
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<tr>
<th>CPP-ACP:</th>
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<tr>
<td>Recaldent™ Mi Paste</td>
<td>Recaldent Pty Ltd./GC America Inc. (<a href="http://www.gcamerica.com">www.gcamerica.com</a>)</td>
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<tr>
<th>HYDROXYAPATITE:</th>
<th>MANUFACTURER</th>
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<tr>
<td>Nani*active</td>
<td>Henkel (<a href="http://www.henkel.com">www.henkel.com</a>)</td>
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Compomers
Compomers contain polyacid-modified monomers with fluoride-releasing silicate glasses and are formulated without water. They are used for restorations in low-stress-bearing areas and for patients at medium risk of developing caries, or when using the sandwich technique. Compomers release fluoride by a mechanism similar to that of glass and hybrid ionomers, but the amount of fluoride release and its duration are less than those of glass and hybrid ionomers. Also, compomers do not recharge from fluoride treatments.48

Giomer
Giomer restorative materials are a hybridization of glass ionomer and resin composite.49 They have the fluoride-release and recharge properties of glass-ionomer cements along with excellent esthetics, easy polishability, and strength of resin composites. Yap et al40 found that while giomer released fluoride, it did not have an initial “burst” type of release like glass ionomers. Their long-term release of fluoride is lower than that of the other materials.

Pit-and-Fissure Sealants
Pit-and-fissure sealants are materials used in preventive dentistry that provide a mechanical barrier against lodgment of bacteria in deep pits and fissures. Available sealants are either resin-based or glass-ionomer-based. Since resin-based sealants do not provide fluoride release, glass-ionomer sealants are more effective for caries prevention. The addition of remineralizing agents such as fluorides and CPP-ACP can further enhance remineralization (Table 1).

Fluorides are incorporated into the fillers (strontium-fluoride-alumosilicate glass) of sealants. Fluoride release occurs through hydrolysis and external and internal diffusion.51 The addition of ACP to resin sealants has made them comparable to glass-ionomer-based sealants.52 Meyers and Eanes showed that the solubility of ACP enables it to release supersaturating levels of calcium and phosphate ions in proportion that is favorable for hydroxyapatite formation.53 ACP-containing sealants have a higher remineralizing capacity with a tendency to remineralize enamel subsurface lesions.24,55

Dentifrices
Dentifrices are one of the most practical methods for delivering remineralizing agents. Fluoride is one of the most commonly used remineralizing agents. Achieving densely filled prism cores, the quality of remineralization following the use of fluoride dentifrice was found to be superior compared to fluoride rinse.54 Fluoride in dentifrice may be available as single-fluoride sourced products (sodium fluoride [NaF], stannous fluoride [SnF2], amine fluoride [AmF], or sodium monofluorophosphate [NaMFP]) or dual-fluoride active products (NaF + sodium monofluorophosphate [SMFP], AmF + SnF2) (Table 2). Products containing NaMFP are said to provide the highest level of fluoride compared to others.57 The addition of xylitol (5%) to fluoride-containing (500 ppm) dentifrice is found to enhance remineralization compared to fluoride alone.58 A recent trend is to incorporate CCP-ACP along with fluoride, which is found to have an additive effect. Burwell and Muscle found that CPP-ACP provided sustained condition for remineralization when used in a dentifrice.21 Additionally, the use of 1,500 ppm fluoridated NaF toothpaste has been found to be more effective on the remineralization process than the use of a 50 ppm NaF mouthrinse.59

Chewing Gums
Chewing gums are an effective method for caries prevention. When chewed for long periods they stimulate saliva and have a washing off effect on debris. They also can be used to carry the...
desired medicaments to the tooth, thus having a multiple benefit. Agents such as fluoride and CPP-ACP are added to improve the anticaries potential of chewing gums (Table 3). Gum arabic, which is the main ingredient of chewing gum, is considered to have an ability to enhance remineralization, probably because of its high concentration of calcium (Ca²⁺). It has been found that chewing gum for about 30 minutes after meals and snacks considerably aided in remineralization.

Cai et al. found that CPP-ACP produced better remineralization even in the presence of citric acid, which means that CPP-ACP can be used to promote remineralization in the presence of an acidic environment. It has also been observed that the effect of xylitol along with calcium lactate improved remineralization.

Pastes, Rinses, and Dental Floss

Pastes used for remineralization contain calcium- and phosphate-realizing components (e.g., CCP-ACP) with or without fluoride. Paste can be applied via prophylactic cup, custom tray, toothbrush, or fingertip. Use of CPP-ACP along with fluoride-containing dentifrice has proved to be beneficial in reducing the demineralization caused by demineralization.

Remineralizing agents such as fluoride, NovaMin, etc, can also be added to the prophylactic paste for additional benefit. Recently, an innovative paste containing a tricalcium phosphate ingredient was introduced that features fluoride along with calcium and phosphate with a protective barrier around the calcium that inhibits its reaction with fluoride ions. As the toothpaste comes in contact with saliva during brushing, the barrier breaks down and makes the calcium, phosphate, and fluoride readily available to the tooth, promoting remineralization.

Mouthrinses (Table 4) are vehicles used to carry various medicaments to the areas of dentition that are difficult to brush. In a study by Reynolds et al, mouthrinse containing CPP-ACP and fluoride has shown to increase fluoride uptake into plaque.

Dental floss is an important adjunct to deliver fluoride to the interproximal areas of teeth. Studies have shown that fluoride can be released from flossing with SnF₂-impregnated dental floss (Table 5), elevating salivary fluoride levels for at least 30 minutes. Thus, use of fluoride-containing dental floss is an alternate option for delivery of fluoride to individuals at risk of dental caries.

FUTURE PROSPECTS

Tissue engineering is the field of functional restoration of tissue structure and physiology for impaired or damaged tissues due to cancer, diseases, and trauma. Contemporarily, this field is also being exploited in dentistry. Regenerative dentistry applies tissue engineering approaches for the repair/regeneration of pulp tissue organ using three basic key elements: an extracellular matrix scaffold (which can be synthetic), progenitor/stem cells, and inductive morphogenetic signals that are exposed to a conductive environment to regenerate a vital and functional tissue and/or organ.

Pulp/stem/progenitor cells, which have the characteristics of extensive self-renewal capacity and maintenance throughout the life of an organism, can be exploited in culturing large numbers of pulp/stem cells in vitro. Morphogens are inductive signals that function as growth/differentiation factors in odontoblast differentiation. Recombinant human BMP2, BMP4, and BMP7 have shown to induce reparative/regenerative dentin formation in vivo. Scaffolds provide a physicochemical surface for the differentiation of odontoblasts from pulp cells. An ideal method would be to fabricate a material using these three basic elements that would mimic apatite crystals. Recently, nanotechniques, nanoscopic tools, and x-ray scanning tomography (XTM) have been used to create a 3-dimensional profile of normal and various dentin microarchitecture (1 µm x 1 µm x 1 µm cube).

Also, synthetic carbonate-hydroxypatite biomimetic

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<th>TABLE 5</th>
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<td><strong>Prophylactic Paste and Floss</strong></td>
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<tr>
<td><strong>PROPHYLACTIC PASTE</strong></td>
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<td><strong>FLUORIDE:</strong></td>
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<tr>
<td>TRADE NAME</td>
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<td>Propil</td>
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<tr>
<td><strong>NOVAMIN:</strong></td>
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<td>TRADE NAME</td>
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<tr>
<td>NuCare™ Prophy Paste</td>
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<td><strong>FLOSS</strong></td>
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<td>TRADE NAME</td>
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<tr>
<td>FlossRx™</td>
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<td><strong>FLUORIDE &amp; SILVER NITRATE:</strong></td>
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<tr>
<td>TRADE NAME</td>
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<td>Silver Care Dental Floss</td>
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(CHA) nanocrystals have been investigated regarding the possibility of obtaining an in vitro remineralization of the altered enamel surfaces. Treatment of demineralized enamel with CHA nanocrystals for just 10 minutes induced a consistent enamel remineralization through the formation of a surface carbonate-hydroxyapatite coating. This coating is caused by the chemical bond of the synthetic CHA nanocrystals onto the surface prismatic hydroxyapatite enamel.

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REFERENCES


The Role of Remineralizing Agents in Dentistry: A Review
Arathi Rao, MDS; and Neeraj Malhotra, MDS, PGDHHM

This article provides 2 hours of CE credit from AEGIS Publications, LLC. Record your answers on the enclosed answer form or submit them on a separate sheet of paper. You may also phone your answers in to (215) 504-1275 x 207 or fax them to (215) 504-1502 or log on to www.dentalaegis.com/ceed and click on “Continuing Education.” Be sure to include your name, address, telephone number, and last 4 digits of your Social Security number.

Pleased see answer form on page 36.

1. Remineralization occurs when:
A. pH rises.
B. pH drops.
C. anaerobic bacteria predominate.
D. carbohydrates break down bacterial covalent bonds.

2. The newly introduced titanium fluoride (TIF) exhibits enhanced uptake of:
A. fluoride.
B. calcium.
C. phosphate.
D. hydroxyapatite.

3. The advantage of CPP-ACP is:
A. the availability of calcium, phosphate, and fluoride in one product.
B. that it will remineralize the sulcular fluid.
C. that it reduces periodontitis.
D. that it reduces halitosis.

4. A nonfermentable sugar alcohol acts as a carrier or reservoir for:
A. potassium chloride.
B. sodium phosphate.
C. calcium phosphates.
D. sodium chloride.

5. Ozone therapy is also proposed to stimulate remineralization of incipient caries following treatment for a period of about:
A. 6 to 8 seconds.
B. 6 to 8 minutes.
C. 6 to 8 hours.
D. 6 to 8 weeks.

6. Glass ionomer (conventional and resin-modified) and compomers:
A. exhibit marginal breakdown with excessive gum chewing.
B. exhibit significant shade change with excessive gum chewing.
C. can be recharged from external sources such as topical fluoride application.
D. require use of fluoride etchants.

7. The addition of what to fluoride-containing (500 ppm) dentifrice is found to enhance remineralization compared to fluoride alone?
A. xylitol (5%)
B. hydroxyapatite (3.2%)
C. strontium (17.5%)
D. phospholipid (5%)

8. Gum arabic, which is the main ingredient of chewing gum, is considered to have an ability to enhance remineralization, probably because of its high concentration of:
A. fluoride (F-).
B. sodium (Na+).
C. iron (Fe-).
D. calcium (Ca2+).

9. Regenerative dentistry applies tissue engineering approaches for the repair/regeneration of pulp tissue organ using which basic key elements:
A. an extracellular matrix scaffold (which can be synthetic).
B. progenitor/stem cells.
C. inductive morphogenetic signals.
D. all of the above

10. Treatment of demineralized enamel with CHA nanocrystals for how long induced a consistent enamel remineralization through the formation of a surface carbonate-hydroxyapatite coating?
A. 10 minutes
B. 10 hours
C. 10 days
D. 10 weeks

The deadline for submission of quizzes is 24 months after the date of publication. Participants must attain a score of 70% on each quiz to receive credit. Participants receiving a failing grade on any exam will be notified and permitted to take one re-examination. Participants will receive an annual report documenting their accumulated credits, and are urged to contact their own state registry boards for special CE requirements.