Remineralization, the Natural Caries Repair Process—The Need for New Approaches
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Remineralization is the natural repair process for caries lesions. We have known about remineralization for at least a hundred years. However, it is only in recent decades that the therapeutic importance of remineralization has been generally accepted. Fluoride delivered topically in various vehicles has proven effective in enhancing remineralization and to be incorporated into the new therapeutic armamentarium to halt or reverse the caries process. There is a need to find ways to enhance the remineralization process and to transfer such knowledge into clinical therapy.

INTRODUCTION: REMINERALIZATION—A NATURAL REPAIR PROCESS FOR CARIES LESIONS

The process of dental caries is now well-understood (Fejerskov et al., 1981; ten Cate and Featherstone, 1991; Featherstone, 2000). We know that acid-producing bacteria in the biofilm on the teeth feed on the fermentable carbohydrates taken into the mouth and produce organic acids (acetic, lactic, etc.) as byproducts (Geddes, 1975). These acids diffuse into the tooth and dissolve the carbonated hydroxyapatite mineral, forming a caries lesion (Silverstone, 1973). If this process continues, cavitation results. Prior to cavitation, a subsurface lesion with partial demineralization is present, and this can be remineralized. Remineralization occurs when calcium and phosphate in the water among the enamel or dentin crystals recrystallize on the surfaces of existing crystal remnants. The calcium and phosphate come primarily from saliva. This process has been known for a long time and in recent decades has been studied extensively (Silverstone, 1973; ten Cate and Duijsters, 1982; Arends and ten Bosch, 1985; Wefel, 1990; ten Cate and Featherstone, 1991; Zero, 1995). We now know that the mineral formed during remineralization is more resistant to acid than the original enamel or dentin mineral, especially if fluoride is present to enhance remineralization and to be incorporated into the new crystal surfaces (ten Cate and Duijsters, 1982; ten Cate and Featherstone, 1991; Featherstone, 1999, 2000). Remineralization is a natural repair process for caries lesions. It requires no growth factors or soft-tissue biological processes. It is simple inorganic chemistry at work.

For a long time, there was debate as to whether the process of remineralization, so elegantly described in many laboratory experiments, really occurred in the mouth. Over the last 25 years or so, many experiments have been done in human mouths that have clearly established that remineralization is a real phenomenon that occurs in the mouth, is enhanced by fluoride, and makes the teeth more resistant to further demineralization (Øgaard and Rølla, 1992; ten Cate and Mundorff-Shrestha, 1995; Zero, 1995).

The natural repair of early lesions through remineralization is understandably a major contributor to the dramatic downturn in the numbers of decayed, missing, and filled teeth over the last 30-40 years, and the increase in the percent of the population that is apparently clinically caries-free. This is illustrated in a paper (Jenkins, 1985) in which the downturn in caries prevalence is attributed to the use of fluoride-containing toothpastes in several countries. That is, in a traditional visual/tactile examination, these individuals have no obvious caries lesions. The increase, over 3 decades, in the percent of teenagers in the USA who were apparently clinically caries-free is illustrated in Fig. 1.

In the early 1970s, the change was rapid, but it leveled off and essentially plateaued in the 1990s. It is likely that a considerable fraction of the teenagers who were apparently caries-free actually had white-spot lesions that had not yet cavitated and were therefore not recorded in these surveys. Although analysis of the latest data indicates that more than 30% of teenagers were apparently caries-free (Fig. 1), the converse of this is that at least 60% of teenagers around 1990, and most likely still today, had observable decay. It is also likely that most of those teenagers had non-cavitated lesions that could have been arrested or even reversed by remineralization therapy. The conclusion that can be drawn from the data is that remineralization, as we currently see it manifested, can deal with only a certain level of caries (acid) challenge. That is, fluoride therapy as we know it now cannot deal completely with a high bacterial challenge. Beyond that, additional measures are needed to overcome the challenge. The

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Remineralization, dental caries, dental enamel.

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The bottom line is that caries continues to be a major health problem in adults and children throughout the world.

CLINICAL FLUORIDE EFFECTIVENESS

Many studies have shown the clinical effectiveness of fluoride in various delivery modes in reducing the levels of dental caries (DePaola et al., 1993). None, however, has shown that fluoride can eliminate decayed surfaces and teeth in all individuals. Reports on the effectiveness of fluoride in the drinking water showed a reduction of about 30%, for example (Newbrun, 1989). Fluoride toothpaste clinical trials showed similar reductions over time when compared with a placebo toothpaste at the time when placebo could still be studied. Large numbers of children and adults continued to have caries lesions, reduced in number, but not eliminated (DePaola et al., 1993).

A more recent study (Curnow et al., 2002) produced a very interesting and key result. Children who had supervised daily toothbrushing with a conventional 1000-ppm-F toothpaste had 56% fewer D3FS (decayed and filled surfaces) lesions in first permanent molars than did unsupervised children. This result clearly illustrates the benefit of frequent applications of fluoride in a conventional toothpaste delivery system. However, in just two years, 29% and 36% had new DFS (decayed and filled surfaces) in the intervention and non-intervention groups, respectively. Therefore, even in the supervised brushing group, a sizable percentage of the children still had new decayed, missing, and filled surfaces, and most likely a high percentage of surfaces with non-cavitated lesions that could be remineralized.

A study with a 5000-ppm-F toothpaste vs. an 1100-ppm-F toothpaste in older adults showed a statistically significant rehardening of 76% of non-cavitated root caries lesions with the higher fluoride content compared with 35% in the 1100-ppm-F group (Baysan et al., 2001). This study again illustrates that fluoride is very effective at enhancing remineralization, but only up to a point.

The conclusion from the above-mentioned studies and others like them is that in persons with a high caries challenge, fluoride is not enough to overcome the challenge. We need either more effective means of remineralization or more effective antibacterial treatment in conjunction with remineralization.

THE CARIES BALANCE CONCEPT

For a better understanding of the nature of the apparently insoluble caries problem, and to come up with the clinical and future research implications, we can consider the concept of the caries balance. This was first proposed by Featherstone in 1999 and is illustrated in Fig. 2.

Several refinements and modifications of the concept have been published since then, with the key elements being three pathological factors and three protective factors (Featherstone, 2004). The components most essential to the present discussion are illustrated in Fig. 2. Remineralization requires calcium and phosphate, which generally comes from saliva. Remineralization is enhanced by fluoride. These are two of the three protective factors in the “caries balance” concept.

It is now well-accepted that the primary modes of action of fluoride are enhancement of remineralization, inhibition of demineralization, and inhibition of plaque bacteria, with remineralization being the most important (ten Cate and Featherstone, 1991). Enhancement of remineralization can occur only with calcium and phosphate being present, from whatever source. (The antibacterial component of the protective side of the balance is addressed by ten Cate [2009].)

Obvious ways to enhance remineralization and to make it more effective are to supply calcium and phosphate, especially when saliva flow is inadequate (Fig. 2), and to deliver fluoride more effectively over longer periods of time.
IMPROVING FLUORIDE ACTION FOR REMINERALIZATION

About 20 years ago, we showed, in laboratory experiments, that fluoride levels above about 0.03 ppm F were sufficient to enhance remineralization, and that levels above 0.1 ppm F were much more effective (Featherstone and Zero, 1992). Since that time, a clinical study reported a 70% reduction in caries vs. non-caries (control) status in high-risk children who wore a fluoride-releasing glass device in their mouths (Toumba and Curzon, 2005). The mean salivary F levels were 0.11 ppm in the test group vs. 0.03 ppm F in the control group over a two-year period. Baseline fluoride levels in saliva from dentifrice or mouthrinse are generally in the 0.02 to 0.04 ppm F level, which is adequate for low- or medium-caries-challenge individuals, but presumably not for high caries challenge (Featherstone and Zero, 1992). Even for currently marketed fluoride varnishes, these salivary fluoride levels are returned to baseline levels within 24 hrs after a varnish application (Eakle et al., 2004).

Fluoride varnish application has been shown in numerous studies to reduce caries incidence. Most recently, a study showed marked caries reductions in young children under the age of 5 yrs, with three applications being better than two and one, respectively (Weintraub et al., 2006). In contrast, 18% of children still manifested new caries lesions in 2 yrs, even with two fluoride varnish applications, and 42% with no varnish application. This illustrates, again, that, in high-risk individuals, fluoride delivered by any of the vehicles currently marketed still leaves many individuals with caries progressing.

One of the conclusions from these laboratory and clinical studies is that there is a major anti-caries effect for high-caries individuals if a “therapeutic level” of fluoride as a background at around 0.1 ppm F in saliva can be achieved day and night. Any additional fluoride delivery, such as twice-daily brushing with a fluoride toothpaste, will be a bonus. A sustained-release device that functions to provide the same protection as the glass device referred to above (Toumba and Curzon, 2005) could be the target, only in a more acceptable form for the affected individuals. Such a device would overcome compliance problems and could be targeted with success to high-caries-risk individuals. It may not eliminate all caries, but would lead to dramatic reductions, and, in concert with antibacterial treatments, might eliminate caries in these individuals.

There are undoubtedly other ways to enhance the action of fluoride by retaining it in the mouth longer and at “therapeutic” concentrations. Now that we understand the process of remineralization, the next step is to put that understanding into the development of new and more effective delivery systems.

CALCIUM AND PHOSPHATE

As described above, calcium and phosphate are necessary for remineralization. Fluoride alone cannot remineralize. In the case of severe salivary dysfunction, rampant caries results if other measures are not taken (Mandel, 1989). Even in less severe salivary hypofunction, it is likely that supplementation with calcium and phosphate will be beneficial, especially if this can be done in conjunction with effective levels of fluoride. Numerous laboratory studies have been reported dealing with solubility of various calcium phosphate salts, degrees of supersaturation, enhancement of remineralization, calcium complexes as carriers, amorphous calcium phosphate, and so on (LeGeros, 1991). When these concepts are extrapolated to the mouth, the situation becomes much more complex because of the presence (or absence) of saliva which is supersaturated with respect to hydroxyapatite, and usually with respect to fluorapatite. With normal salivary composition and flow, it is likely that sufficient calcium and phosphate are present, and that additional amounts of these components will not be useful.

However, in the case of reduced salivary function, it is likely that there is a major preventive and reparative role for agents that supplement the action of fluoride, especially by supplying calcium and phosphate in soluble and available forms that can be transported into subsurface lesions. Numerous studies have shown the potential benefits of some cheeses in enhancing remineralization in the mouth. Studies that will be summarized at this meeting have been conducted for many years with these concepts and have established the potential of calcium phosphopeptides to enhance remineralization (Reynolds, 2009).

There are undoubtedly other approaches that can be taken to enhance the role of calcium and phosphate in remineralization.

CONCLUSIONS

Dental caries continues to be a major health problem in adults and children. Fluoride delivered through drinking water, dentifrices, mouthrinses, and varnish has had a major impact in reducing dental caries incidence, primarily in Western countries, over the last 30 years. Fluoride in its present delivery forms is insufficient to overcome high caries challenge in many individuals. Improved and more effective delivery of fluoride at the right amounts and for prolonged periods of time is possible. Calcium and phosphate delivery can be enhanced to improve remineralization, especially in persons with reduced salivary function. There is a great need for improved and novel remineralization methods to alter the caries balance for the better, especially in individuals with a high cariogenic bacterial challenge.

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