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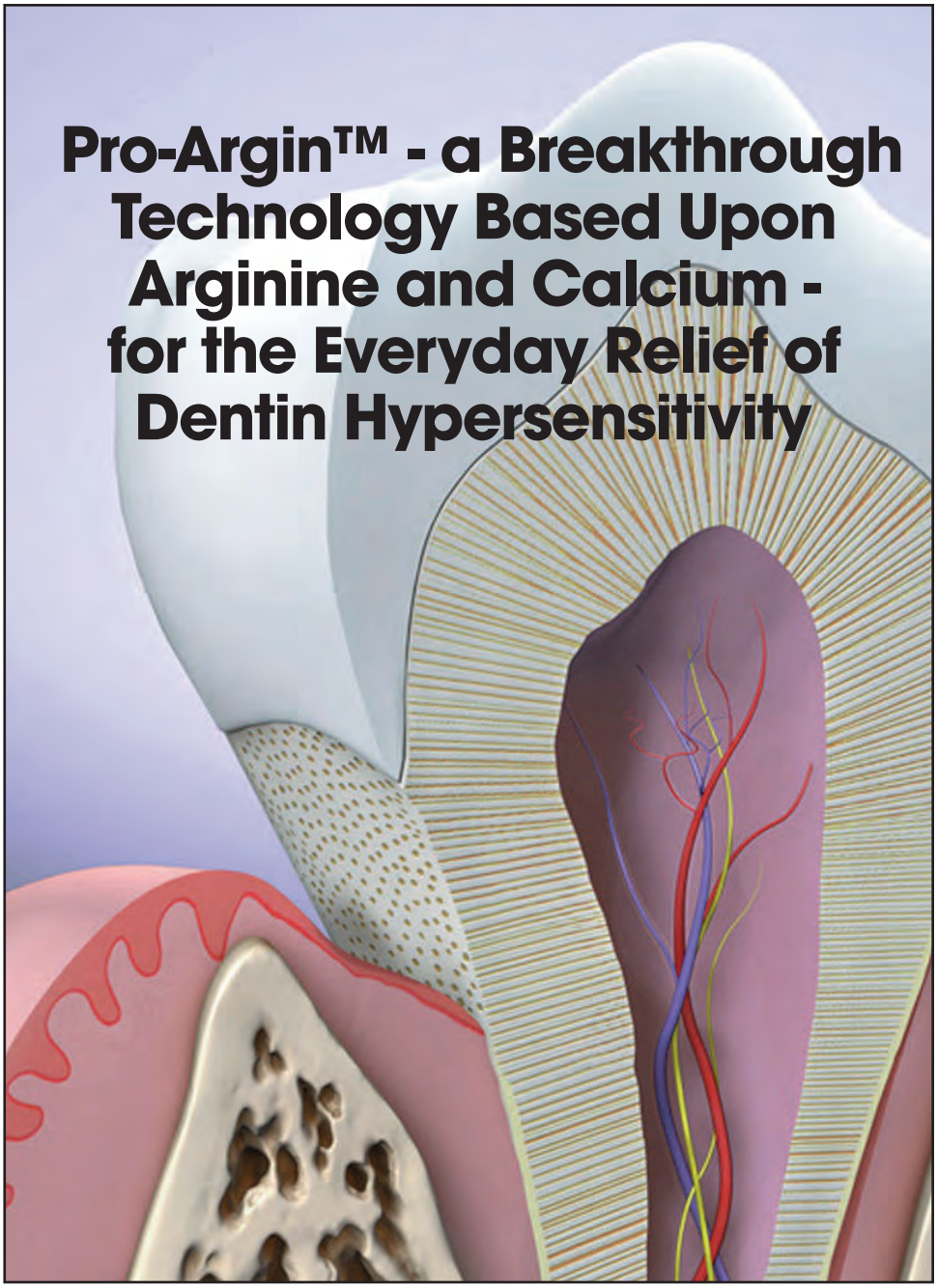

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Dentin Hypersensitivity: From Diagnosis to a Breakthrough Therapy for Everyday Sensitivity Relief

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Abstract

This paper provides an overview of the current knowledge of diagnosis, epidemiology, etiology, and clinical management of dentin hypersensitivity. It summarizes technical approaches to relieve sensitivity in professional and home-use products, with emphasis on the clinical evidence for the efficacy of desensitizing toothpaste, and introduces a new innovative dentifrice technology containing 8% arginine, calcium carbonate, and 1450 ppm fluoride.

Dentin hypersensitivity is characterized by short, sharp pain arising from exposed dentin in response to external stimuli which cannot be ascribed to any other form of dental defect or disease. The hydrodynamic theory proposes that pain-producing stimuli cause a change in dentin fluid flow that activates intra-dental nerve fibers, via a mechanoreceptor response, to cause pain. To be hypersensitive, dentin must be exposed and dentin tubules must be open to external stimuli and patent at the pulp. Gingival recession is the primary cause of dentin exposure, and a major predisposing factor for dentin hypersensitivity.

Dentin hypersensitivity is a prevalent condition. It has been reported to afflict 15–20% of the adult population, typically 20 to 50-year-olds, with peak incidence between 30 and 39 years. Some studies have reported higher prevalence levels of up to 57%. The incidence of dentin hypersensitivity is expected to rise with changing diets, and as caries and periodontal disease prevention result in improved oral health status, and retention and functionality of the dentition.

Treatments to relieve dentin hypersensitivity are based on interruption of the neural response to pain stimuli or occlusion of open tubules to block the hydrodynamic mechanism. Effective and robust dentin occlusion offers the greatest prospect for instant and lasting relief of dentin hypersensitivity. In particular, materials which can coat exposed dentin surfaces, in addition to plugging and sealing open dentin tubules, offer the intriguing prospect of strengthening dentin and rendering it less susceptible to predisposing factors, while concurrently reducing dentin hypersensitivity.

Clinical studies have shown that a new toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate offers significantly increased efficacy in reducing sensitivity, compared to a market-leading toothpaste containing 2% potassium ion. Mechanism of action studies have shown that this technology physically seals dentin tubules with a plug that contains arginine, calcium carbonate, and phosphate. This plug, which is resistant to normal pulpal pressures and to acid challenge, effectively reduces dentin fluid flow and, thereby, reduces sensitivity.

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Introduction

Dentin hypersensitivity is a common oral health problem affecting one or more teeth of many adult individuals on a global basis. Indeed, there is a growing awareness that dentin hypersensitivity is an increasingly important issue to be addressed, both from a diagnostic and a problem-management perspective, as caries prevention and periodontal disease management measures become increasingly successful, resulting in improved oral health status and functionality of the dentition throughout life.[1]

Dentin hypersensitivity was first discussed more than a century ago when Gysi attempted to explain "the sensitiveness of dentin," and described the phenomenon of fluid movement in dentin tubules.[2] More than sixty years later, Brännström proposed the "hydrodynamic theory" as a mechanism to explain the transmission of pain-producing stimuli of the dentin.[3,4] Other theories have been proposed as potential mechanisms by which pain transmission can occur, but these have largely been discounted.[5,6]

In 1982, dentin hypersensitivity was described as an enigma, because it was frequently encountered and poorly understood.[7] The past twenty-five years have witnessed an evolution in the scientific understanding of this condition. Largely based on a suggestion in 1983,[8] the term "dentin hypersensitivity" was formally defined in 1997 in the guidelines for clinical trials.[9] This definition was officially accepted in 2003, with one minor change, by the Canadian Advisory Board on Dentin Hypersensitivity in their consensus-based recommendations for the diagnosis and management of dentin hypersensitivity.[10] Clearly, the condition is no longer the enigma that was once described. Nonetheless, there is a need for continued basic and clinical research that will lead to improved prevention and management of dentin hypersensitivity.[5]

Today, dozens of in-office sensitivity treatments and mass market sensitivity relief toothpastes are available worldwide. Clinical studies demonstrate the effectiveness of some in-office products, *e.g.*, 5% sodium fluoride varnish;[11] nonetheless, there is a paucity of data on the majority of these products.[5,12] There appears to be a significant body of clinical data to support the efficacy of potassium-based dentifrices, and these products have been acknowledged to provide relief to their users.[13] However, some authors have concluded that the data are equivocal.[6,13] Despite the reported prevalence of dentin hypersensitivity, it is noteworthy that a relatively small percentage of sufferers seek professional treatment to alleviate their condition and/or use an everyday sensitivity relief toothpaste.[10]

This review has identified a number of opportunities to improve prevention and management of dentin hypersensitivity:

first, by building understanding of the science of dentin hypersensitivity; second, by communicating the risk factors associated with dentin hypersensitivity to the profession and consumers, and how to reduce risk and prevent damage that can lead to dentin hypersensitivity; and third, by developing and validating truly effective professional and home-use sensitivity relief products.

This paper provides a brief overview of the diagnosis, etiology, and epidemiology of dentin hypersensitivity, its clinical management, and products to alleviate the condition. In addition, it introduces the development and validation of a novel sensitivity relief technology based upon arginine and calcium carbonate. The following two papers in this Special Issue, by Ayad, *et al*. and Docimo, *et al.*, report the results of two eight-week clinical studies on a new dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate. These studies demonstrate superior sensitivity relief of this dentifrice to a market-leading dentifrice containing 2% potassium ion as the antisensitivity agent. The final paper, by Petrou, *et al.*, presents evidence of the mechanism of action of the arginine-calcium carbonate technology in forming a solid plug to physically seal open dentin tubules, thereby stopping fluid movement and reducing sensitivity.

From Definition to Diagnosis of Dentin Hypersensitivity

Largely based upon an understanding developed in 1983,[8] the definition of dentin hypersensitivity was proposed in 1997[9] and, with one minor amendment, was adopted in 2003.[10] The current definition states "Dentin hypersensitivity is characterized by short, sharp pain arising from exposed dentin in response to stimuli, typically thermal, evaporative, tactile, osmotic, or chemical, and which cannot be ascribed to any other form of dental defect or disease."[5,10] In 2002, the European Federation of Periodontology adopted the term "root sensitivity" to describe tooth sensitivity associated with the treatment of periodontal disease, because of the uncertainty of whether this form of sensitivity is truly dentin hypersensitivity.[5]

An important consequence for clinicians of the definition of dentin hypersensitivity is that great care must be taken to perform differential diagnosis to exclude all other dental defects or diseases that might give rise to similar presentations of dental pain. The factors to consider in performing the diagnosis of dentin hypersensitivity, such as dental caries, split tooth or cracked cusp, medication issues, and bleaching sensitivity, have been described in detail elsewhere.[5,13,14] Suffice it to say that differential diagnosis and the correct attribution of dental pain to dentin hypersensitivity are essential to assess appropriate treatment options for this, as well as other painful conditions.[13,15]

Sensitivity Mechanisms, Etiology, and Predisposing Factors in Dentin Hypersensitivity

The most frequently experienced pain from dentin hypersensitivity is characterized by a rapid onset, sharp burst of pain of short duration (seconds or minutes), associated with A-beta and A-delta nerve responses to stimuli.[5,6,16]

The hydrodynamic theory is now accepted as the mechanism by which dentin hypersensitivity occurs, and suggests that dentin hypersensitivity is a result of movement of fluid within the dentin tubules. Most pain-producing stimuli, in particular the most problematic cold and evaporative stimuli, cause an outflow of dentin fluid.[5,17,18] This results in a pressure change across the dentin which activates intra-dental nerve fibers, via a mechano-receptor response, to cause pain. In addition, the fluid movement in the tubules can cause an electrical discharge, known as "streaming potential," which may contribute by electrically stimulating a nerve response.[5] In contrast, heat causes a relatively slow retreat of dentin fluid, and the resultant pressure changes activate the nerve fibers in a less dramatic fashion, consistent with the fact that heat is generally a less problematic stimulus than cold.[5]

The hydrodynamic mechanism requires that dentin tubules are open at the dentin surface and patent to the pulp. Scanning electron microscopy and dye penetration studies of exfoliated teeth, with clinically characterized "sensitive" and "non-sensitive" areas of exposed dentin, have shown that tubules are greater in number (eight times), larger in diameter (two times), and are open in "sensitive" teeth, whereas tubules are fewer in number, smaller in diameter, and are usually blocked in their "non-sensitive" counterparts.[19,20] As the rate of fluid flow through dentin tubules is proportional to the fourth power of the tubule radius, it is highly likely that the difference in tubule diameter between "sensitive" and "non-sensitive" teeth is of clinical relevance to the treatment of dentin hypersensitivity.[5] Interestingly, it is also reported that the number and diameter of dentin tubules increases from the outer surface of dentin through to the inner junction with the pulp, which suggests that dentin hypersensitivity could worsen as dentin is progressively lost through tooth wear.[5]

For dentin hypersensitivity to occur, dentin must become exposed (a process termed "lesion localization") and dentin tubules must be opened and patent to the pulp (a process termed "lesion initiation").[5,12] These two processes are multi-factorial.

One important route through which dentin can become exposed is gingival recession. Gingival recession is a multi-factorial condition rendered more complex by anatomical factors.[21] Overzealous tooth brushing and improper tooth brushing technique have been associated with gingival damage and loss of gingival tissue through mechanical forces.[5] On the other hand, periodontal disease and related periodontal conditions, along with surgical and non-surgical treatment procedures, have been associated with periodontal tissue damage and loss of gingival tissue through biological breakdown processes.[22] Once gingival recession occurs, by either means, the cementum covering the dentin surface is easily removed by physical and/or chemical forces, thereby exposing the underlying dentin.[5]

A second route through which dentin can become exposed is enamel loss. New research into the mechanical and chemical processes of tooth wear has shown that abrasion and acid erosion can exacerbate enamel loss. Detailed *in vitro* and *in situ* studies have shown that the mechanical process of brushing with a toothbrush alone has no measurable effect on enamel, and that tooth brushing with toothpaste contributes little, if anything, to the loss of enamel over a lifetime of use.[5] In contrast, the chemical process of erosion from acidic foods and drinks can result in significant tooth wear and exposure of dentin on any aspect of the tooth surface.[5,12] Importantly, dentin exposure which results from

enamel loss in sites predisposed to dentin hypersensitivity, *i.e.*, in the cervical area, is believed to result from dietary acid erosion in combination with tooth brushing.[23,24] *In vitro* mechanistic studies have demonstrated that exposure of enamel to extrinsic acids results in a direct loss of surface mineral, as well as in enamel surface softening,[25,26] and that this fragile surface-softened tissue can be readily removed by low levels of physical force.[27] Clinical experience suggests that gingival recession, rather than cervical enamel loss, is the main cause of dentin exposure and is, therefore, the key pre-disposing factor for dentin hypersensitivity.[5]

Dentin is naturally protected, and exposed dentin tubules are occluded by a coating known as the "smear layer," which comprises protein components and calcium phosphate deposits derived from saliva. In principle, any physical or chemical force which can remove the smear layer can open the dentin tubules and initiate a hypersensitive lesion. Addy has suggested, based upon *in vitro* studies, that tooth brushing with toothpaste can physically remove the smear layer and open up exposed dentin tubules.[5] However, dedicated clinical studies validating these *in vitro* observations are not evidenced in the literature. In contrast, currently available clinical data suggest that physical removal of the smear layer and the opening of exposed dentin tubules is not a key factor during normal tooth brushing. On the other hand, there seems to be little doubt that acidic foods and drinks are able to remove the dentin smear layer, reducing its protective effects, and to soften dentin, rendering the surface-softened dentin tissue susceptible to physical forces, such as tooth brushing. Current evidence suggests that acid erosion is an important factor in opening exposed dentin tubules; abrasion, however, can have an exacerbating effect.[5,17]

Prevalence of Dentin Hypersensitivity

Dentin hypersensitivity can present as early as adolescence, but it is more typically found in the adult population.[17] Studies of the prevalence of dentin hypersensitivity have reported widely differing levels, ranging from 4–57% in individuals within general dental practice settings.[5,12,13,17] These wide variations have been attributed to a number of factors, including the method of assessment or diagnosis, the population base and setting, and behavioral factors, such as oral hygiene habits and intake of acidic foods and drinks. A large pan-continental survey, conducted in 2002, showed self-reported levels of sensitivity in the range 37–52%,[28] whereas a series of earlier surveys have suggested a prevalence of approximately 15%.[29] It has also been reported that perceived levels of dentin hypersensitivity vary among different professionals, with hygienists perceiving almost twice the levels perceived by dentists.[10] Experts have suggested that patient surveys overestimate the prevalence of dentin hypersensitivity, as carefully conducted clinical examinations by trained dental examiners have provided consistently lower prevalence levels.[5,30-32] However, a recent summary of studies showed a broader range of prevalence values (4-74%) for studies using clinical diagnosis.[33] Not surprisingly, levels of root sensitivity are higher, ranging from 60-98% in patients following periodontal treatment.[5,13,22]

It appears that there is a slightly higher incidence of dentin hypersensitivity in females than in males, which may reflect oral hygiene and dietary practices. The major portion of sufferers is currently in the age range 20–49 years, with peak incidence between 30–39 years.[5,13] Reduced levels of dentin hypersensitivity in older individuals are most likely a result of reparative processes which decrease permeability and reduce hydraulic conductance, such as the formation of secondary dentin.[17] Buccal cervical regions of the permanent teeth are most commonly affected, and there is an indication that the canine, pre-molar, and incisor teeth are more frequently affected than the molar teeth.[5] This distribution of dentin hypersensitivity is remarkably consistent with the predilection for gingival recession. Once again, this suggests that gingival recession is the primary cause of dentin exposure and a major predisposing factor for dentin hypersensitivity.[5,13]

The Clinical Management of Dentin Hypersensitivity

In stark contrast to caries and periodontal disease, the management of which are based upon decades of research and well-established, evidence-based prevention and treatment measures, dentin hypersensitivity has been managed on an empirical basis. Furthermore, approaches to dentin hypersensitivity management have focused heavily upon treatment, with little emphasis, to date, on prevention.

The advances in scientific understanding which have occurred over the past twenty years, now allow a more comprehensive approach to dentin hypersensitivity management that encompasses the control of its etiological and predisposing factors. Indeed, management strategies have been proposed which include: 1) correct diagnosis, compatible with the clinical description of dentin hypersensitivity, based upon history and examination; 2) differential diagnosis, to exclude other conditions which might give rise to similar pain; 3) treatment of all secondary conditions that induce symptoms similar to dentin hypersensitivity; 4) identification of etiologic and predisposing factors, particularly dietary and oral hygiene habits pertinent to erosion and abrasion; 5) removal or minimization of etiologic and predisposing factors through dietary advice and oral hygiene instruction; and 6) recommendation or provision of treatment based upon individual needs.[5]

Particularly pertinent to this paper is stage 6 of this proposed management strategy, *i.e.*, the treatment of dentin hypersensitivity based upon individual needs. A first step is to recommend use of a desensitizing toothpaste, because this typically results in improvement for the majority of individuals. When use of a desensitizing toothpaste is insufficient, home-use prescription fluoride products can offer additional benefits to sensitivity relief toothpaste, and so may be a useful second step; professionally applied products may be suitable for patients with additional treatment needs.[10]

Products to Alleviate Dentin Hypersensitivity

Two treatment approaches have been used to provide relief of dentin hypersensitivity: one is to interrupt the neural response to pain stimuli; the other is to occlude open tubules to block the hydrodynamic mechanism.

The principle of interrupting the neural response to pain stimuli has primarily been applied to the development and validation of desensitizing toothpaste. Today, desensitizing toothpastes

represent 8–10% of the global toothpaste market. The vast majority of these products contain a potassium salt to "numb" the pain of dentin hypersensitivity.[34,35] Most potassium-based toothpastes also contain fluoride for cavity protection; some contain other ingredients to provide additional benefits, such as tartar control and whitening

The United States Food and Drug Administration (FDA) has reviewed clinical data on the efficacy of 5% potassium nitrate toothpaste and, on the basis of its safety and proven efficacy in reducing dentin hypersensitivity, has classified potassium nitrate toothpaste as a safe and effective tooth desensitizer in the tentative final monograph.[36] Potassium nitrate (5%), potassium chloride (3.75%), and potassium citrate (5.5%) are used interchangeably in desensitizing toothpaste in many countries, as each of these salts provides 2% potassium ion which is the desensitizing active ingredient.

In clinical trials, potassium-based toothpastes have been shown to take at least two weeks of twice daily use to yield measurable reductions in sensitivity, and longer time periods, generally four to eight weeks, to demonstrate significant levels of pain relief. Clinical data support that all three forms of potassium, nitrate,[37-42,45,47-52] chloride,[43,44] and citrate,[45,46] are effective in reducing dentin hypersensitivity as compared to a regular fluoride toothpaste. Clinical studies have also shown that the addition of fluoride to a potassium-based toothpaste, for cavity prevention, does not negatively impact the sensitivity relief efficacy.[40-42,44] Likewise, clinical studies have shown that the addition of other benefit agents, such as plaque and tartar control ingredients, to potassium-based toothpaste does not impact efficacy.[47-49] A summary of these clinical studies is given in Table I.

This review has identified published evidence that supports potassium-containing toothpaste formulations as effective in reducing dentin hypersensitivity. However, some clinical investigators have reported that potassium-based toothpastes are no more effective than regular fluoride toothpaste,[53-55] suggesting that clinical evidence in support of the efficacy of potassium-based desensitizing toothpaste is equivocal.[6,13,56,57] Differences in clinical results can be attributed to diversity among clinical protocols and the well-known placebo or Hawthorne effect. The fact that placebo products can reduce sensitivity by as much as 40% from baseline has significantly impacted the ability to differentiate the efficacy of a test product in some studies.[6,57]

The principle of occluding open tubules to block the hydrodynamic mechanism has been broadly applied to professional in-office and home-use products.[58] However, it has found limited application in desensitizing toothpaste. Strontium chloride (10%) was the first tubule-blocking ingredient used in toothpaste. It can still be found in a few brands in some markets, but it has largely been surpassed by the introduction of potassium. For this reason, there is a paucity of clinical data on the efficacy of strontium chloride products. The few studies that are available are summarized in Table I. These data support the conclusion that strontium chloride toothpaste is less effective in reducing dentin hypersensitivity than potassium nitrate toothpaste.[50-52] Stannous fluoride has also been used in some desensitizing products. Anhydrous gel and toothpaste formulations have been shown to be effective in reducing sensitivity as compared to placebo control products.[59-64] Typically, these formulations have been shown to provide significant reductions in dentin hypersensitivity after four weeks of twice daily use.[59-62] There are no published direct head-to-head studies comparing the efficacy of potassium versus stannous as a desensitizing agent. Despite its proven efficacy, stannous fluoride has not been widely available in the sensitive toothpaste market. There are a number of reasons for this, among which are its well-known negatives of tooth staining and poor taste. Both strontium and stannous are believed to work by precipitating insoluble metal compounds on dentin surfaces, thereby partially occluding open dentin tubules. In contrast to the arginine-calcium carbonate technology described in this Special Issue and summarized below, strontium and stannous products do not provide a solution to dentin hypersensitivity by encouraging deposition of "natural" calcium and phosphate.

The Development and Validation of a Novel Sensitivity Relief Technology

Recent advances in understanding the etiology of dentin hypersensitivity have led to recognition of the importance of designing new treatments that will target the underlying causes, as well as treat the symptoms of dentin hypersensitivity. It has been suggested that future research should focus on developing and validating new materials that can render the dentin surface significantly more resistant to mechanical and chemical attack. Specifically, it has been proposed that increasing the surface mineral density of dentin could improve resistance to wear, whereas plugging and sealing open tubules with a calcium- and phosphate-containing, dentin-like substance would increase wear resistance, as well as increase acid resistance by blocking diffusion through the tubules into the dentin sub-surface.

In a recent review of biological approaches to therapy, it was proposed that the ideal dentin hypersensitivity treatment would mimic the natural desensitizing process that takes place without intervention, and leads over time to spontaneous occlusion of open dentin tubules. The authors suggested that a successful treatment should render treated dentin non-sensitive and sclerotic, such a state being more desirable than open, patent, sensitive dentin. They concluded that any treatment that completely seals dentin tubules will restore that surface to a healthy state.[6]

Saliva plays a role in naturally reducing dentin hypersensitivity; first, by transporting calcium and phosphate into dentin tubules to induce tubule plugging; and second, by forming a surface protective layer of salivary glycoprotein with calcium and phosphate. Alkaline pH favors both of these processes, and so salivary factors that maintain slightly alkaline pH *in vivo* have been suggested to favor occlusion. While natural processes are insufficient to induce rapid occlusion and reduce dentin hypersensitivity in most individuals, investigations into the science underpinning these mechanisms have resulted in the development of a new "saliva-based composition" for treating dentin hypersensitivity.[65] The essential components of this technology are arginine, an amino acid which is positively charged at physiological pH, *i.e.*, pH 6.5–7.5, bicarbonate, which is a pH buffer, and calcium carbonate, which is a source of calcium. A product based upon this composition (ProClude®, Ortek Therapeutics, Roslyn Heights, NY, USA) has recently been marketed in the

Table I
Summary of Published Clinical Studies Supporting the Efficacy of Desensitizing Toothpaste Containing Potassium

Reference	Test Product(s)	Control Product(s)	Study Duration	Outcome Measures	Result
Tarbet, *et al.* 1980[37]	5% KNO_3	Placebo	4 weeks	Electrical and cold air	5% KNO_3 > control ($p < 0.05$) at 2, 3, 4 weeks
Nagata, *et al.* 1994[38]	5% KNO_3	Placebo	12 weeks	Tactile, air blast and subjective	5% KNO_3 > control ($p < 0.05$) at 4, 8, 12 weeks
Schiff, *et al.* 1998[39]	KNO_3 + 1500 ppm MFP	Placebo	8 weeks	Tactile and air blast	5% KNO_3 > control ($p < 0.0001$) at 4, 8 weeks
Silverman 1985[40]	KNO_3 ± MFP	Placebo	12 weeks	Tactile, air blast and subjective	5% KNO_3 ± F > control at 2, 4, 8, 12 weeks; NS between KNO_3 products
Council on Dental Therapeutics 1982[41]	KNO_3 ± MFP	Placebo	12 weeks	Tactile and air blast	5% KNO_3 ± F > control at 2, 4, 8, 12 weeks; NS between KNO_3 products
Silverman, *et al.* 1988[42]	5% KNO_3 ± 1000 ppm MFP	1000 ppm MFP and non-F control	12 weeks	Tactile and variable temp air	5% KNO_3 ± F > controls at 12 weeks ($p < 0.01$); NS between KNO_3 products
Salvato, *et al.* 1992[43]	3.75% KCl + 1000 ppm MFP	Placebo	12 weeks	Tactile, air blast and subjective	5% KCl > control ($p < 0.05$) at 4, 8, 12 weeks*
Silverman, *et al.* 1994[44]	3.75% KCl ± 1000 ppm MFP	Placebo	8 weeks	Tactile, air blast and subjective	3.75% KCl ± F > controls at 4, 8 weeks ($p < 0.05$); NS between KCl products
Chesters, *et al.* 1992[45]	5.5% KCitrate + MFP	5% KNO_3 + MFP and MFP control	8 weeks	Electrical, tactile and air blast	Logit transformation shows K Cit > KNO_3 > control ($p < 0.05$) at 3, 8 weeks
Hu, *et al.* 2004[46]	5.5% KCitrate + 1450 ppm MFP + high cleaning silica	3.75% KCl + 0.3% triclosan + 1450 ppm NaF	8 weeks	Tactile and air blast	Test = control at 4, 8 weeks
Schiff, *et al.* 1994[47]	5% KNO_3 + 1100 ppm NaF + pyrophosphate and copolymer	Placebo	12 weeks	Tactile, air blast and subjective	Test > control ($p < 0.01$) at 6, 12 weeks**
Ayad, *et al.* 1994[48]	5% KNO_3 + 1100 ppm NaF + pyrophosphate and copolymer	KNO_3 + 1000 ppm MFP	12 weeks	Tactile, air blast and subjective	Test = control at 6, 12 weeks
Wara-aswapati, *et al.* 2005[49]	5% KNO_3 + 0.3% triclosan + 1000 ppm MFP	5% KNO_3 + 1000 ppm MFP and 1000 ppm MFP	12 weeks	Tactile and air blast (+ PI and GBI)	NS between KNO_3 products; Both KNO_3 products > control ($p < 0.05$) at 12 weeks
Tarbet, *et al.* 1982[50]	10% Sr Cl_2 (and others)	5% KNO_3	4 weeks	Electrical and cold air	5% KNO_3 > 10% Sr Cl_2 ($p < 0.05$) at 1, 2, 3, 4 weeks
Kanapka 1982[51]	10% Sr Cl_2 (and others)	5% KNO_3	4 weeks	Electrical and cold air	5% KNO_3 > 10% Sr Cl_2 ($p < 0.05$) at 1, 2, 3, 4 weeks
Silverman, *et al.* 1996[52]	5% KNO_3 + 1100 ppm NaF and 10% Sr Cl_2	5% KNO_3 and 1100 ppm NaF	8 weeks	Tactile, air blast and subjective	5% KNO_3 ± F > F control at 4, 8 weeks ($p < 0.02$); NS between 10% Sr Cl_2 and control; 5% KNO_3 ± F > 10% Sr Cl_2 at 8 weeks ($p < 0.05$)***

*KCl not significant on tactile measure only at 4 weeks.
**SS at $p < 0.1$ at 12 weeks only on subjective measure.
***KNO_3 not significant on tactile measure only.

United States for the management of tooth sensitivity during professionally administered prophylaxis treatment. Clinical studies[65] have shown that this desensitizing prophylaxis paste is effective in providing instant sensitivity relief when burnished onto sensitive teeth following scaling and root planing procedures, and that this sensitivity relief lasts for at least 28 days following a single treatment. In addition, *in vitro* studies of the mechanism of action have demonstrated tubule occlusion.[65] The composition has also been incorporated into toothpaste (marketed in the United States as DenClude®, Ortek Therapeutics, Roslyn Heights, NY, USA) for use at home following professional treatment.

The Colgate-Palmolive Company has further developed this innovative technology by combining the key components, arginine and calcium carbonate, with fluoride. During the first stage

of this development, an experimental toothpaste containing 4% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate was shown to be effective in reducing dentin hypersensitivity in two clinical studies, the results of which are summarized in this paper and presented in Tables II–V below.

The first of these studies was a two-week, double-blind, parallel group, randomized clinical study in which this experimental (placebo) toothpaste with 4% arginine was compared to a matched control toothpaste without arginine.[66] Seventy subjects completed the study. There were no significant differences in tactile (test = 12.00 ± 4.57 and control = 12.14 ± 5.04) and air blast (test = 2.47 ± 0.44 and control = 2.31 ± 0.44) sensitivity scores between the test and control products at baseline. The two-week scores from this study are given in Tables II and III. The results show that the experimental toothpaste with 4% arginine provided statistically significant reductions in tactile (42.0%) and air blast (50.6%) sensitivity scores compared to the control product after two-weeks' use.

Table II
Summary of the Two-Week Tactile Sensitivity Scores for Subjects Who Completed the Two-Week Clinical Study

		Two-Week	Within Treatment Analysis		Between Treatment Comparison	
Treatment	n	Summary (Mean ± SD)	Percent Change[3]	Sig.[4]	Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	35	35.46 ± 11.14	193.8%	p < 0.05	42.0%	p < 0.05
Placebo Dentifrice[2]	35	24.97 ± 11.14	106.9%	p < 0.05		

[1]Colgate® Sensitive Toothpaste containing 4.0% arginine and 1450 MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA).
[2]Colgate® Fluoride Toothpaste containing 1450 MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA).
[3]Percent change exhibited by the two-week mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the two-week examination.
[4]Significance of paired t-test comparing the baseline and two-week examinations.
[5]Difference between two-week means expressed as a percentage of the two-week mean for the Placebo Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 4.0% arginine relative to the Placebo Dentifrice.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

Table III
Summary of the Two-Week Air Blast Sensitivity Scores for Subjects Who Completed the Two-Week Clinical Study

		Two-Week	Within Treatment Analysis		Between Treatment Comparison	
Treatment	n	Summary (Mean ± SD)	Percent Reduction[3]	Sig.[4]	Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	35	0.86 ± 1.75	64.0%	p < 0.05	50.6%	p < 0.05
Placebo Dentifrice[2]	35	1.74 ± 1.75	27.2%	NS		

[1]Colgate® Sensitive Toothpaste containing 4.0% arginine and 1450 MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA).
[2]Colgate® Fluoride Toothpaste containing 1450 MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA).
[3]Percent change exhibited by the two-week mean relative to the baseline mean. A positive value indicates a reduction in air blast sensitivity at the two-week examination.
[4]Significance of paired t-test comparing the baseline and two-week examinations.
[5]Difference between two-week means expressed as a percentage of the two-week mean for the Placebo Dentifrice. A positive value indicates a reduction in air blast sensitivity for the Test Dentifrice containing 4.0% arginine relative to the Placebo Dentifrice.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

The second of these two studies[66] was an eight-week, double-blind, parallel group, randomized clinical study in which the same experimental toothpaste with 4% arginine was compared to a currently marketed desensitizing toothpaste, Sensodyne® Total Care F toothpaste (GlaxoSmithKline, Middlesex, UK), containing 3.75% potassium chloride and 1450 ppm fluoride as sodium fluoride (NaF), as a positive control. Seventy-nine subjects completed the study. There were no significant differences in tactile (test = 12.63 ± 3.75 and control = 12.05 ± 3.76) and air blast (test = 2.56 ± 0.43 and control = 2.64 ± 0.38) sensitivity scores between the test and control products at baseline. The eight-week scores from this study are given in Tables IV and V. The results show that the experimental toothpaste with 4% arginine provided statistically significant reductions in tactile (14.7%) and air blast (27.0%) sensitivity scores compared to the control product after eight-weeks' use.

Table IV
Summary of the Eight-Week Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

		Eight-Week	Within Treatment Analysis		Between Treatment Comparison	
Treatment	n	Summary (Mean ± SD)	Percent Change[3]	Sig.[4]	Percent Difference[5]	Sig[6]
Test Dentifrice[1]	40	45.75 ± 6.11	270.7%	p < 0.05	14.7%	p < 0.05
Control Dentifrice[2]	39	39.87 ± 6.11	223.1%	p < 0.05		

[1]Colgate® Sensitive Toothpaste containing 4.0% arginine and 1450 MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA).
[2]Sensodyne® Total Care F (GlaxoSmithKline, Middlesex, UK).
[3]Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the eight-week examination.
[4]Significance of paired t-test comparing the baseline and eight-week examinations.
[5]Difference between eight-week means expressed as a percentage of the eight-week mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 4.0% arginine relative to the Control Dentifrice.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

Table V
Summary of the Eight-Week Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

		Eight-Week	Within Treatment Analysis		Between Treatment Comparison	
Treatment	n	Summary (Mean ± SD)	Percent Reduction[3]	Sig.[4]	Percent Difference[5]	Sig[6]
Test Dentifrice[1]	40	0.54 ± 0.46	79.2%	p < 0.05	27.0%	p < 0.05
Control Dentifrice[2]	39	0.74 ± 0,46	71.5%	p < 0.05		

[1]Colgate® Sensitive Toothpaste containing 4.0% arginine and 1450 MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA).
[2]Sensodyne® Total Care F (GlaxoSmithKline, Middlesex, UK).
[3]Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates a reduction in air blast sensitivity at the eight-week examination.
[4]Significance of paired t-test comparing the baseline and eight-week examinations.
[5]Difference between eight-week means expressed as a percentage of the eight-week mean for the Control Dentifrice. A positive value indicates a reduction in air blast sensitivity for the Test Dentifrice containing 4.0% arginine relative to the Control Dentifrice.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

To meet the objective of providing superior dentin hypersensitivity efficacy relative to currently marketed desensitizing toothpaste after two weeks of twice-daily brushing, a new formula with 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate has been developed. The new formula was validated in two dentin hypersensitivity clinical trials,[67,68] and in mechanism of action studies[69] which are summarized below and discussed in detail in the articles which follow.

The two clinical studies both demonstrated that the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride provides superior sensitivity relief relative to a market-leading dentifrice containing 2% potassium ion, as 3.75% potassium chloride. In an eight-week study in Canada, the 8% arginine toothpaste provided statistically significant reductions in dentin hypersensitivity in response to tactile (16.2%, 22.4%, and 21.4%) and air blast (16.2%, 29.2%, and 63.4%) measures compared to Sensodyne Total Care F at two, four, and eight weeks, respectively.[67] Likewise, in an eight-week study in Italy, the same 8% arginine toothpaste provided statistically significant reductions in dentin hypersensitivity in response to tactile (37.0%, 30.0%, and 12.2%) and air blast (23.9%, 32.0%, and 29.3%) measures compared to Sensodyne Total Care F at two, four, and eight weeks, respectively.[68] These two clinical studies show remarkable consistency in their results, demonstrating superior efficacy in reducing dentin hypersensitivity of a dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride compared to a market-leading dentifrice containing 2% potassium ion at two, four, and eight weeks, on both tactile and air blast measures.

Several state-of-the-art imaging methods have been used to elucidate aspects of the mechanism of action of the arginine-calcium carbonate technology. Confocal Laser Scanning Microscopy (CLSM) studies have demonstrated that the desensitizing prophylaxis paste with 8% arginine and the dentifrice with 8% arginine have the same mechanism of action, and that both are highly effective in occluding open dentin tubules. No dentin occlusion was observed with control toothpastes; one containing calcium carbonate alone, the other containing 8% arginine and an alternative calcium abrasive, dicalcium phosphate dihydrate (Dical). CLSM studies, using fluorescein isothiocyanate (FITC) dye binding to locate arginine, have shown that arginine is delivered to the inner surfaces of dentin tubules within the occluded dentin plug. Additionally, CLSM studies have shown that the occlusion achieved is resistant to acid challenges,[69] such as carbonated beverages.

High resolution Scanning Electron Microscopy (SEM) images have confirmed that the desensitizing prophylaxis paste provides complete occlusion of open dentin tubules, and freeze-fracture images have shown that the plug reaches a depth of two microns into the tubule. Chemical mapping of the occluded surfaces using Energy Dispersive X-ray (EDX) has shown that the material on the dentin surface and occluded within the dentin tubules primarily consists of calcium and phosphate. Studies using Electron Spectroscopy for Chemical Analysis (ESCA) have provided quantitative data which have confirmed these observations and, in addition, have identified the presence of carbonate.[69]

Atomic Force Microscopy (AFM) has been used to further substantiate the blocking mechanism. Images of untreated specimens showed the helical fine structure of the inter-tubular dentin, as well as tubules that were completely open. Images of specimens treated with the desensitizing prophylaxis paste showed that the helical structure on the dentin surface was no longer visible as a result of surface coating, and the tubules were sealed shut.[69]

Together, these results have clearly demonstrated that both the desensitizing prophylaxis paste with 8% arginine and the dentifrice with 8% arginine reduce dentin hypersensitivity by sealing and plugging dentin tubules. Kleinberg has suggested that arginine physically adsorbs onto the surface of the calcium carbonate *in vivo*, forming a positively charged agglomerate which readily binds to the negatively charged dentin on the exposed surfaces and within the tubules. In addition, Kleinberg has suggested that the pH of the arginine-calcium carbonate agglomerate is sufficiently alkaline to facilitate natural intervention through deposition of calcium and phosphate from saliva and/or dentin fluid.[65] The results of the mechanism of action studies, summarized here and presented in detail in the paper by Petrou, *et al*.,[69] are consistent with Kleinberg's hypotheses, and support that the interaction of arginine and calcium carbonate *in vivo* triggers the deposition of phosphate, in addition to arginine, calcium, and carbonate on the dentin surface and within the dentin tubules.[69]

Finally, hydraulic conductance experiments have examined whether treatment with the toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride is effective not only in occluding dentin tubules, but also in blocking fluid movement to inhibit the hydrodynamic mechanism. These experiments showed that sequential treatments with the toothpaste resulted in reductions in dentin permeability of 63% after one treatment and 82% after 14 treatments. Furthermore, these studies showed that the dentin occlusion is robust, as reduced permeability was maintained after seven days of pulpal pressure (79%) and after treatment with strong acid (77%).[69]

Summary and Conclusions

This paper provides an overview of the current state of knowledge of the diagnosis, epidemiology, etiology, and clinical management of dentin hypersensitivity. It summarizes technical approaches to relieve sensitivity in professional and home use products, with special emphasis on the clinical evidence for the efficacy of desensitizing toothpaste, and introduces a new innovative dentifrice technology based upon arginine and calcium carbonate.

Gingival recession, a complex multi-factorial condition, is the primary cause of exposed dentin and a major predisposing factor for dentin hypersensitivity. Enamel erosion caused by acidic foods and drinks can contribute to dentin exposure, although it appears to play a secondary role to gingival recession in exposing dentin at the cervical margin. However, acid erosion almost certainly plays a more important role in opening exposed dentin tubules.

Two treatment approaches have been used to provide relief of dentin hypersensitivity; one is to interrupt the neural response to pain stimuli, and the other is to occlude open tubules to block

the hydrodynamic mechanism. Effective and robust dentin occlusion offers the greatest prospect for instant and lasting relief of dentin hypersensitivity. Specifically, it has been proposed that increasing the surface mineral density of dentin could improve resistance to wear, whereas plugging and sealing open tubules with a calcium- and phosphate-containing tooth mineral-like substance would increase wear resistance, as well as increase acid resistance by blocking diffusion into the dentin sub-surface.[6] These two effects, taken together, could strengthen the dentin and render it less susceptible to predisposing factors, especially acid erosion, thereby reducing the risk of dentin hypersensitivity.

A new innovative technology based upon arginine and calcium carbonate has been developed and validated as a unique and highly effective treatment for dentin hypersensitivity. Clinical data from two independent studies show that a toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate offers superior efficacy in reducing sensitivity as compared to a leading desensitizing dentifrice containing 2% potassium ion as the desensitizing agent. Mechanism of action studies have demonstrated that this innovative technology works by physically sealing dentin tubules with a plug that contains arginine, calcium carbonate, and phosphate. This plug, which is resistant to normal pulpal pressures and to acid challenge, effectively reduces dentin fluid flow and, thereby, reduces sensitivity.

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Comparing the Efficacy in Reducing Dentin Hypersensitivity of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride to a Commercial Sensitive Toothpaste Containing 2% Potassium Ion: An Eight-Week Clinical Study on Canadian Adults

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Abstract

- **Objective:** This paper presents the results of one of two eight-week dentin hypersensitivity clinical studies in which the efficacy of a novel toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) was compared to that of a benchmark commercial toothpaste containing 2% potassium ion, dosed as 3.75% potassium chloride, and 1450 ppm fluoride as sodium fluoride (NaF).
- **Methods:** An eight-week clinical study, with seventy-seven patients, was conducted in Mississauga, Canada using a double-blind, stratified, two-treatment design. Tactile sensitivity assessments, as well as air blast sensitivity assessments, were used to compare the efficacy of the two products.
- **Results:** This clinical study demonstrated that the new toothpaste, containing 8.0% arginine and 1450 ppm MFP in a calcium carbonate base, provided a significant reduction in dentin hypersensitivity when used over a period of eight weeks. The study also showed that this new arginine toothpaste provided significantly greater reductions ($p < 0.05$) in dentin hypersensitivity in response to tactile (16.2%, 22.4%, and 21.4%) and air blast (16.2%, 29.2%, and 63.4%) stimuli than the benchmark commercial toothpaste containing 2% potassium ion and 1450 ppm NaF in a silica base, after two, four, and eight weeks of product use, respectively.
- **Conclusion:** A new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), provides significantly greater hypersensitivity relief ($p < 0.05$) compared to a commercial sensitive toothpaste containing 2% potassium ion after two, four, and eight weeks of product use.

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Introduction

Dentin hypersensitivity is characterized by a sharp pain which arises from exposed dentin in response to an external stimulus, and cannot be explained by any other form of dental pathology. The responsible trigger for such discomfort is usually a thermal (cold temperature), tactile (toothbrush or dental instrument), osmotic (sweet), or dehydrating (air blast) stimulus.[1] Dentin hypersensitivity is typically experienced when the root of the tooth has been exposed to the oral environment as a result of gingival recession. Gingival recession may occur naturally, compounded by poor oral hygiene habits, especially overzealous tooth brushing, or it may result from surgical or non-surgical periodontal treatment. Dentin hypersensitivity occurs more frequently in the cervical area of the roots, where the cementum is very thin. Periodontal procedures, such as scaling and root planing, may entirely remove this thin cementum layer and induce root hypersensitivity. As people live longer, healthier lives and maintain their dentitions, there will be an increased demand on dental professionals to manage the sensitivity of cervically exposed dentin, as well as any secondary issues that may arise from the discomfort associated with dentin hypersensitivity. In particular, dentin hypersensitivity may render tooth brushing more difficult in some individuals, with the result that persistent and continued accumulation of dental plaque may increase the incidence of caries, gingivitis, and more serious periodontal problems.[2]

Several theories have been proposed to explain the mechanism of dentin hypersensitivity, including the odontoblast transducer theory, the dentin receptor theory, and the hydrodynamic theory.[3,4] Scientific evidence supports the hydrodynamic theory and, for this reason, it is generally favored by the dental community. The hydrodynamic theory[5] (modified by Brännström[6] in 1963) assumes that fluid movement within the dentin tubules is the basis for the transmission of painful sensations. Specifically, it proposes that non-noxious stimuli at the tooth surface cause fluid movement within the dentin tubules, affecting the pulpal mechanoreceptors and resulting in the sensation of pain. In 1994, Nähri, *et al*.[7] provided an addendum to the hydrodynamic theory,

suggesting that the perception and sensation of pain was directly related to the stimulation of the nerves within the pulp via electrical current.

Regardless of the etiology, the problem needs to be addressed in order to provide patients with improved oral comfort and quality of life. To this end, a number of agents have been proposed to help control dentin hypersensitivity and relieve discomfort; some can be used by the patient at home, others must be applied in the dental office by a dental professional. One approach by which this can be achieved is to reduce the diameter of open dentin tubules in order to limit the displacement of fluids within them (decreased hydrodynamic flow), thereby blocking neurotransmission and decreasing the response to painful stimuli. According to Trowbridge and Silver,[8] this could be achieved by forming a smear layer on the exposed dentin, using topical agents that form insoluble precipitates within the tubules, or by blocking the entrance to tubules with plastic resins. This approach has been most extensively applied in professionally administered products.

The most common products used by patients to relieve pain from dentin hypersensitivity are desensitizing dentifrices; specifically, toothpastes containing potassium salts. Potassium salts (*i.e.*, potassium nitrate, potassium citrate, and potassium chloride) have been used extensively as desensitizing agents, based upon a second approach to relief of discomfort. In effect, the potassium ion is believed to have a depolarizing effect on electrical nerve conduction, causing nerve fibers to be less excitable to the stimuli,[9] thereby reducing the patient's sensation of pain.

Arginine, an amino acid, has been identified as an ingredient with potential oral health benefits. Kleinberg showed that a combination of arginine bicarbonate and calcium carbonate is able to be deposited on exposed dentin surfaces to physically block and seal open dentin tubules.[10] This concept has recently been further evaluated by the Colgate-Palmolive Company, and a novel toothpaste has been developed containing arginine in a calcium carbonate base with 1450 ppm fluoride as sodium monofluorophosphate. Clinical studies have demonstrated that this toothpaste is highly effective in reducing dentin hypersensitivity, and *in vitro* mechanism of action studies have shown that this novel technology works by occluding dentin tubules.[11]

The objective of this eight-week clinical trial was to compare the efficacy in reducing dentin hypersensitivity of a new toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA) to a commercial sensitive toothpaste containing 2% potassium ion as 3.75% potassium chloride, and 1450 ppm fluoride as NaF in a silica base (Sensodyne® Total Care F toothpaste, GlaxoSmithKline, Middlesex, UK) over an eight-week period. This study essentially replicates an eight-week study conducted in Italy, which is reported in the following paper in this issue.[12]

Materials and Methods

This eight-week, single-center, parallel-group, double-blind, stratified, and randomized clinical study was conducted in the Canadian Clinical Research Center in Mississauga, Canada. Subjects were recruited from the patient population of the center, as well as by advertisement. Seventy-seven patients (25 males, 52 females with a mean age of 35.2 ± 10.6 years) were selected based on the following criteria:

- Subjects had to be between 18 and 70 years of age, in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.
- Subjects were required to possess a minimum of two hypersensitive teeth which were anterior to the molars and demonstrated cervical erosion/abrasion or gingival recession, and for which a tactile hypersensitivity stimulus score of 10–50 grams of force (Yeaple probe) and an air blast stimulus score of 2 or 3 (Schiff Cold Air Sensitivity Scale) were presented at the baseline examination.
- Subjects needed to be available for the duration of the study, and to sign an informed consent form.
- Teeth that were abutments for partial dentures and teeth exhibiting extensive or defective restorations, caries, fractures, excessive mobility, or suspected pulpal pathology were not included in the study.
- Subjects that had orthodontic appliances, more than one incisor with a prosthetic crown or veneer, tumors of the soft or hard oral tissues, moderate or advanced periodontal disease, or more than one carious lesion were excluded from the study.
- Subjects were also excluded from the study if they were concurrently using medications including analgesics with a potential to mask pain sensation, or if they had used commercially available desensitizing agents within the three months prior to the study.
- Pregnant women and individuals who were participating in another clinical trial were also excluded.

Qualifying subjects were stratified according to baseline tactile and air blast sensitivity scores, and were randomly assigned within strata to one of the following two study treatments: the new toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride (Test Dentifrice group) or Sensodyne Total Care F toothpaste (Control Dentifrice group). Both toothpastes were provided in original tubes, over-wrapped with opaque white paper to ensure the double-blind design. Subjects were also given a soft bristle toothbrush and instructed to brush their teeth twice a day (morning and evening) for one minute each time. A log of the dispensed products was kept, and all clinical supplies were refurbished as needed.

After the baseline evaluation, subjects were re-evaluated at three days, and at two, four, and eight weeks. At each time point, they received a thorough oral examination of their hard and soft tissues, followed by a careful evaluation of their dentin hypersensitivity using the Yeaple probe and the air/water syringe.

All examinations were performed by the same investigator throughout the study.

Tactile Sensitivity Assessment

Tactile sensitivity was assessed using a calibrated Model 200A Yeaple Electronic Pressure Sensitive Probe (Yeaple Research, Pittsford, NY, USA). Scores were recorded in terms of a quantified reproducible force (grams).[13-15] After presetting the force to 10 grams, the probe tip was passed over the exposed dentin on the buccal surface of the selected teeth, apical to the cemento-enamel junction. Subsequent passes were made, each time with

the applied force increased by 10 grams, until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams had been reached. A force of 50 grams was considered the cut-off point; higher scores on this index correspond to lower levels of dentin hypersensitivity.

Air Blast Sensitivity Assessment

Air blast sensitivity was assessed by directing a one-second blast of air onto the exposed buccal root surface of the sensitive tooth, from a distance of one centimeter, using the air component of a dental air/water syringe. After shielding the adjacent proximal teeth from the air blast through the placement of two fingers, the air blast was applied with a pressure of 60 p.s.i. (± 5 p.s.i) and a temperature of 70°F (± 3°F) for one second.

Sensitivity was recorded in accordance with the air sensitivity scale as described by Schiff, *et al.*[15] as follows:

0 = Tooth/Subject sensitivity does not respond to air stimulation;
1 = Tooth/Subject responds to air stimulus, but does not request discontinuation of stimulus;
2 = Tooth/Subject responds to air stimulus, and requests discontinuation or moves from stimulus;
3 = Tooth/Subject responds to stimulus, considers stimulus to to be painful, and requests discontinuation of the stimulus.

Only teeth with a score of 2 or 3 were selected at the baseline examination since the higher the score, the higher the sensitivity.

Statistical Methods

Statistical analyses were performed separately for the tactile sensitivity assessments and air blast sensitivity assessments. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using an independent t-test. Within-treatment comparisons of the baseline versus follow-up tactile sensitivity and air blast sensitivity scores were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted tactile sensitivity and air blast sensitivity scores at the follow-up examinations were performed using Analyses of Covariance (ANCOVA). All statistical tests of hypotheses were two sided, and employed a level of significance of $\alpha = 0.05$.

Results

All seventy-seven (77) subjects complied with the protocol and completed the eight-week clinical study. A summary of the demographics of the study population is presented in Table I. The treatment groups did not differ significantly with respect to age characteristics.

Throughout the study, there were no adverse events on the soft or hard tissues of the oral cavity which were observed by the examiner, or reported by the subjects when questioned.

Baseline Data

Table II presents a summary of the mean tactile and air blast scores measured at the baseline examination for those subjects who completed the clinical study. For tactile sensitivity, the mean baseline scores were 14.08 for the Test Dentifrice group and 13.46 for the Control Dentifrice group. For air blast sensitivity, the mean baseline scores were 2.67 for the Test Dentifrice group and 2.64 for the Control Dentifrice group. No statistically significant difference was indicated between the treatment groups with respect to either sensitivity score at baseline.

Table I
Summary of Age and Gender
for Subjects Who Completed the Clinical Study

	Number of Subjects			Age	
Treatment	Male	Female	Total	Mean	Range
Test Dentifrice[1]	18	20	38	34.92	18–66
Control Dentifrice[2]	7	32	39	35.51	18–61

[1]Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2]Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.

Table II
Summary of the Baseline Tactile and Air Blast Sensitivity Scores
for Subjects Who Completed the Eight-Week Clinical Study

Parameter	Treatment	n	Baseline Scores (Mean ± SD)[3]
Tactile Sensitivity	Test Dentifrice[1]	38	14.08 ± 6.24
	Control Dentifrice[2]	39	13.46 ± 5.52
Air Blast Sensitivity	Test Dentifrice[1]	38	2.67 ± 0.35
	Control Dentifrice[2]	39	2.64 ± 0.30

[1]Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2]Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3]No statistically significant difference was indicated between the two treatment groups at baseline with respect to either mean tactile sensitivity or mean air blast sensitivity scores.

Three-Day Data

Tactile Sensitivity. Table III presents a summary of the baseline-adjusted mean tactile sensitivity scores measured after

Table III
Summary of the Three-Day Baseline-Adjusted
Mean Tactile Sensitivity Scores for Subjects
Who Completed the Eight-Week Clinical Study

		Baseline-adjusted Tactile Sensitivity Scores	Within Treatment Analysis		Between Treatment Comparison	
Treatment	n	(Mean ± SD)	Percent Change[3]	Sig.[4]	Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	38	13.77 ± 0.00	0.00%	NS	0.00%	NS
Control Dentifrice[2]	39	13.77 ± 0.00	0.00%	NS		

[1]Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2]Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3]Percent change exhibited by the three-day baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the three-day examination.
[4]Significance of paired t-test comparing the baseline and three-day examinations.
[5]Difference between three-day baseline-adjusted means expressed as a percentage of the three-day baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

three days of product use. The three-day baseline-adjusted mean tactile sensitivity scores were 13.77 for the Test Dentifrice group, and 13.77 for the Control Dentifrice group. The percent changes from baseline were 0.0% for the Test Dentifrice group, and 0.0% for the Control Dentifrice group, neither of which was statistically significantly different from baseline.

There was no statistically significant difference indicated between the treatment groups with respect to baseline-adjusted mean tactile sensitivity scores after three days of product use.

Air Blast Sensitivity. Table IV presents a summary of the baseline-adjusted mean air blast sensitivity scores measured after three days of product use. The three-day baseline-adjusted mean air blast sensitivity scores were 2.64 for the Test Dentifrice group, and 2.66 for the Control Dentifrice group. The mean percent reductions from baseline were 0.5% for the Test Dentifrice group, and 0.0% for the Control Dentifrice group, both of which were not statistically significantly different from baseline.

Table IV
Summary of the Three-Day Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	38	2.64 ± 0.06	0.50%	NS	0.80%	NS
Control Dentifrice[2]	39	2.66 ± 0.06	0.00%	NS		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the three-day baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the three-day examination.
[4] Significance of paired t-test comparing the baseline and three-day examinations.
[5] Difference between three-day baseline-adjusted means expressed as a percentage of the three-day baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

There was no statistically significant difference indicated between the treatment groups with respect to baseline-adjusted mean air blast sensitivity scores after three days of product use.

Two-Week Data

Tactile Sensitivity. Table V presents a summary of the baseline-adjusted mean tactile sensitivity scores measured after two weeks of product use. The two-week baseline-adjusted mean tactile sensitivity scores were 23.12 for the Test Dentifrice group, and 19.90 for the Control Dentifrice group. The percent changes from baseline were 68.0% for the Test Dentifrice group, and 44.5% for the Control Dentifrice group, both of which were statistically significantly different from baseline.

Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 16.2% improvement in baseline-adjusted mean tactile sensitivity scores after two weeks of product use.

Table V
Summary of the Two-Week Baseline-Adjusted Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Tactile Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	38	23.12 ± 6.87	68.0%	$p < 0.05$	16.2%	$p < 0.05$
Control Dentifrice[2]	39	19.90 ± 6.87	44.5%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the two-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the two-week examination.
[4] Significance of paired t-test comparing the baseline and two-week examinations.
[5] Difference between two-week baseline-adjusted means expressed as a percentage of the two-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Air Blast Sensitivity. Table VI presents a summary of the baseline-adjusted mean air blast sensitivity scores measured after two weeks of product use. The two-week baseline-adjusted mean air blast sensitivity scores were 1.86 for the Test Dentifrice group, and 2.22 for the Control Dentifrice group. The mean percent reductions from baseline were 30.0% for the Test Dentifrice group, and 16.6% for the Control Dentifrice group, both of which were statistically significantly different from baseline.

Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 16.2% reduction in baseline-adjusted mean air blast sensitivity scores after two weeks of product use.

Table VI
Summary of the Two-Week Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	38	1.86 ± 0.41	30.0%	$p < 0.05$	16.2%	$p < 0.05$
Control Dentifrice[2]	39	2.22 ± 0.41	16.6%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the two-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the two-week examination.
[4] Significance of paired t-test comparing the baseline and two-week examinations.
[5] Difference between two-week baseline-adjusted means expressed as a percentage of the two-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Four-Week Data

Tactile Sensitivity. Table VII presents a summary of the baseline-adjusted mean tactile sensitivity scores measured after four weeks of product use. The four-week baseline-adjusted mean tactile sensitivity scores were 36.21 for the Test Dentifrice group, and 29.59 for the Control Dentifrice group. The percent changes from baseline were 163.0% for the Test Dentifrice group, and 115.9% for the Control Dentifrice group, both of which were statistically significantly different from baseline.

Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 22.4% improvement in baseline-adjusted mean tactile sensitivity scores after four weeks of product use.

Table VII
Summary of the Four-Week Baseline-Adjusted Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Tactile Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	38	36.21 ± 6.75	163.0%	$p < 0.05$	22.4%	$p < 0.05$
Control Dentifrice[2]	39	29.59 ± 6.75	115.9%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the four-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the four-week examination.
[4] Significance of paired t-test comparing the baseline and four-week examinations.
[5] Difference between four-week baseline-adjusted means expressed as a percentage of the four-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Air Blast Sensitivity. Table VIII presents a summary of the baseline-adjusted mean air blast sensitivity scores measured after four weeks of product use. The four-week baseline-adjusted mean air blast sensitivity scores were 1.09 for the Test Dentifrice group, and 1.54 for the Control Dentifrice group. The mean percent reductions from baseline were 59.0% for the Test Dentifrice group, and 41.9% for the Control Dentifrice group, both of which were statistically significantly different from baseline.

Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 29.2% reduction in baseline-adjusted mean air blast sensitivity scores after four weeks of product use.

Table VIII
Summary of the Four-Week Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	38	1.09 ± 0.35	59.0%	$p < 0.05$	29.2%	$p < 0.05$
Control Dentifrice[2]	39	1.54 ± 0.35	41.9%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the four-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the four-week examination.
[4] Significance of paired t-test comparing the baseline and four-week examinations.
[5] Difference between four-week baseline-adjusted means expressed as a percentage of the four-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Eight-Week Data

Tactile Sensitivity. Table IX presents a summary of the baseline-adjusted mean tactile sensitivity scores measured after eight weeks of product use. The eight-week baseline-adjusted mean tactile sensitivity scores were 47.34 for the Test Dentifrice group, and 39.00 for the Control Dentifrice group. The percent changes from baseline were 243.8% for the Test Dentifrice group, and 183.2% for the Control Dentifrice group, both of which were statistically significantly different from baseline.

Table IX
Summary of the Eight-Week Baseline-Adjusted Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Tactile Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	38	47.34 ± 3.35	243.8%	$p < 0.05$	21.4%	$p < 0.05$
Control Dentifrice[2]	39	39.00 ± 3.35	183.2%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the eight-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the eight-week examination.
[4] Significance of paired t-test comparing the baseline and eight-week examinations.
[5] Difference between eight-week baseline-adjusted means expressed as a percentage of the eight-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 21.4% improvement in baseline-adjusted mean tactile sensitivity scores after eight weeks of product use.

Air Blast Sensitivity. Table X presents a summary of the baseline-adjusted mean air blast sensitivity scores measured after eight weeks of product use. The eight-week baseline-adjusted mean air blast sensitivity scores were 0.34 for the Test Dentifrice group, and 0.93 for the Control Dentifrice group. The mean percent reductions from baseline were 87.2% for the Test

Table X
Summary of the Eight-Week Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	38	0.34 ± 0.39	87.2%	$p < 0.05$	63.4%	$p < 0.05$
Control Dentifrice[2]	39	0.93 ± 0.39	65.2%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the eight-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the eight-week examination.
[4] Significance of paired t-test comparing the baseline and eight-week examinations.
[5] Difference between eight-week baseline-adjusted means expressed as a percentage of the eight-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Dentifrice group, and 65.2% for the Control Dentifrice group, both of which were statistically significant.

Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 63.4% reduction in baseline-adjusted mean air blast sensitivity scores after eight weeks of product use.

Discussion

Dentin hypersensitivity is a relatively common problem seen in daily clinical practice. It is characterized by a sharp, transient pain in response to a sensory stimulus that affects eating, drinking, brushing teeth, and breathing.[16] This condition affects nearly 40 million Americans,[17] approximately one in five adults, and can be seen in all age groups.[18] Patients who have received periodontal therapy are four times more at risk of developing hypersensitivity than the general population.[19] Epidemiologic research suggests that prevalence peaks between 30 and 40 years of age, and that women experience a higher incidence of dentin hypersensitivity at a younger age than men.[18] As individuals retain their dentitions for longer and as diets change, it is reasonable to expect that there will be a higher incidence of oral complaints related to dentin hypersensitivity, and with that an increase in requests for treatment.

Potassium salts have been added to dentifrices as sensitivity reducing agents for many years. There is a body of clinical evidence that demonstrates that potassium-based toothpastes are effective in reducing dentin hypersensitivity; however, some investigators have suggested that potassium-based toothpastes are no more effective than regular fluoride toothpaste.[20] In addition, the exact mechanism of action is not completely clear. It is believed that delivering and maintaining a high level of extracellular potassium ions deep in the dentin tubules and around the nerve endings causes depolarization of nerve fiber membranes and prevents repolarization.[9]

A second route that has been investigated by the dental research community is to occlude dentin tubules, or at least reduce their diameter, with a technology that coats the dentin surface and fills the openings of the tubules. This approach has primarily been used to manage sensitivity in the form of products applied by dental professionals using either a varnish or precipitates.[21] Such an approach impairs or limits the displacement of fluids in the dentin tubule, *i.e.*, hydrodynamic flow, and results in the blockage of painful stimuli. While several *in vitro* studies have shown occlusion of dentin tubules with calcium phosphate,[21-24] there is a paucity of clinical data proving efficacy *in vivo*.

An essential amino acid, arginine, first isolated from a lupin seedling extract in 1886 by the Swiss chemist Ernst Schultze, has been investigated in combination with bicarbonate and calcium carbonate for its ability to occlude dentin tubules and reduce pain from dentin hypersensitivity.[10] This technology has recently been further developed by the Colgate-Palmolive Company and validated in a toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate.[20]

The results from the present clinical investigation clearly show that the new toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride and Sensodyne Total Care F toothpaste, containing 2% potassium ion as potassium chloride, were both effective in treating dentin hypersensitivity when used twice daily for a period of eight weeks. Importantly, this clinical study also demonstrates that this new arginine toothpaste provides a level of relief of dentin hypersensitivity that is significantly better ($p < 0.05$) than Sensodyne Total Care F toothpaste after two, four and eight weeks of use.

The results of this clinical study, together with the results of a similar study conducted in Italy and reported in the following paper in this issue,[12] confirm the superior efficacy of the new arginine-calcium carbonate toothpaste in treating dentin hypersensitivity compared to Sensodyne Total Care F toothpaste.

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Comparing the Efficacy in Reducing Dentin Hypersensitivity of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride to a Commercial Sensitive Toothpaste Containing 2% Potassium Ion: An Eight-Week Clinical Study in Rome, Italy

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Abstract

- **Objective:** This paper presents the results of one of two eight-week dentin hypersensitivity clinical studies in which the efficacy of a novel toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) was compared to that of a benchmark commercial toothpaste containing 2% potassium ion, dosed as 3.75% potassium chloride, and 1450 ppm fluoride as sodium fluoride (NaF).
- **Methods:** An eight-week clinical study, with eighty patients, was conducted in Rome, Italy using a double-blind, stratified, two-treatment design. Tactile sensitivity assessments, as well as air blast sensitivity assessments, were used to compare the efficacy of the two products.
- **Results:** This clinical study showed that the new toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base provided a significant reduction in dentin hypersensitivity when used over a period of eight weeks. The study also showed that this new arginine toothpaste provided significantly greater reductions ($p < 0.05$) in dentin hypersensitivity in response to tactile (37.0%, 30.0%, and 12.2%) and air blast (23.9%, 32.0%, and 29.3%) stimuli than the commercial sensitive toothpaste containing 2% potassium ion and 1450 ppm fluoride as NaF in a silica base, after two weeks, four weeks, and eight weeks of product use, respectively.
- **Conclusion:** A new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) provides significantly increased dentin hypersensitivity relief ($p < 0.05$) compared to a commercial sensitive toothpaste containing 2% potassium ion after two weeks, four weeks, and eight weeks of product use.

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Introduction

Dentin hypersensitivity is distinguished as a sudden pain arising from exposed dentin that cannot be explained by any other form of dental pathology. This pain is generally triggered by an external stimulus, such as a thermal (cold temperature), tactile (toothbrush or dental instrument), osmotic (sweet), or evaporative (air blast) stimulus.[1] Dentin hypersensitivity is a common problem in adult populations, and it may well increase as people live and maintain their dentitions longer. As a consequence, there is a significant demand on dental professionals to manage dentin hypersensitivity, as well as address any secondary issues that may arise from its associated discomfort. More specifically, dentin hypersensitivity may render tooth brushing very difficult in some individuals, with the result that persistent and continued accumulation of dental plaque in hypersensitive areas may increase the risk of cavities, gingival inflammation, and further periodontal

problems.[2] Dentin hypersensitivity is a common problem in patients with chronic periodontal disease because the root surface can become exposed as part of the disease process, or as a result of periodontal treatment. In fact, dentin hypersensitivity occurs most frequently in the cervical area of the root, where the cementum is very thin. Periodontal procedures, such as scaling and root planing, may entirely remove this thin cementum layer and induce hypersensitivity.

Several theories have been proposed over the years to explain the mechanism of dentin hypersensitivity.[3,4] Whereas each of these theories has been scientifically investigated, the hydrodynamic theory is the only one that has stood the test of time and, as such, is generally favored by the dental community to explain hypersensitivity. In essence, the hydrodynamic theory[5] (modified by Brännström[6] in 1963) attributes fluid movement within exposed dentin tubules to the transmission of painful sensations. Specifically, non-noxious stimuli at the tooth surface can trigger fluid movement within the dentin tubules affecting the pulpal mechanoreceptors and resulting in the sensation of pain. In 1994, Nähri, *et al*.[7] added to the hydrodynamic theory by suggesting that the perception and sensation of pain are directly related to the stimulation of the nerves within the pulp via electrical current.

Regardless of the etiology, the problem of dentin hypersensitivity needs to be addressed in order to provide patients with improved oral comfort and quality of life. The clinical management of the condition varies widely from products that are applied by the dental professional in office, such as varnishes (resins), to everyday home-use products, the most common of which are desensitizing toothpastes. The products share the same goal: to relieve the patient's discomfort. One approach to accomplish this goal is to limit the possibility of fluid displacement within dentin tubules (decrease hydrodynamic flow) by reducing the diameter of exposed tubules, blocking neurotransmission, and decreasing the response to painful stimuli. According to Trowbridge and Silver,[8] this could be achieved by forming a smear layer on the exposed dentin, either by the use of topical agents that form insoluble precipitates within the tubules, or by blocking the entrance to tubules with plastic resins. Another approach, which has become popular and convenient for the patient, is the use of potassium salts in desensitizing toothpastes. Potassium nitrate, potassium citrate, and potassium chloride have each been used extensively and universally as desensitizing agents. Clinical and mechanism of action studies have shown that 2% potassium ion is the active entity, and this can be dosed as any one of the three commonly used salts. In effect, the potassium ion is believed to have a depolarizing effect on electrical nerve conduction, causing nerve fibers to be less excitable to external stimuli,[9] thereby reducing the patient's sensation of pain.

Arginine, an amino acid, has been studied by Kleinberg and coworkers for its potential oral health benefits. Specifically, a combination of arginine bicarbonate and calcium carbonate has been shown to deposit on exposed dentin surfaces to physically block and seal open dentin tubules.[10] This concept has recently been further evaluated by the Colgate-Palmolive Company, and a novel toothpaste was developed containing 8% arginine in a calcium carbonate base, with 1450 ppm fluoride as sodium monofluorophosphate. Clinical studies have demonstrated that this toothpaste is highly efficacious in reducing dentin hypersensitivity, and *in vitro* mechanism of action studies have shown that this novel technology works by occluding dentin tubules.[11]

The objective of this clinical study was to compare the efficacy in reducing dentin hypersensitivity of a new toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA; Test Dentifrice) to a commercial sensitive toothpaste containing 2% potassium ion, as 3.75% potassium chloride, and 1450 ppm fluoride as NaF in a silica base (Sensodyne® Total Care F toothpaste, GlaxoSmithKline, Middlesex, UK; Control Dentifrice) over an eight-week period. This study essentially replicates an eight-week clinical study conducted in Canada, which was reported in the previous paper in this issue.[12]

Materials and Methods

This eight-week, single-center, parallel-group, double-blind, stratified, and randomized clinical study was conducted in a private practice setting in Rome, Italy. Subjects were recruited from the patient population in a nearby hospital, as well as by advertisement. Eighty patients (24 males and 56 females with a mean age of 42.2 ± 10.6 years) were selected based on the following criteria:

- Subjects had to be between 18 and 70 years of age, in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.
- Subjects were required to possess a minimum of two hypersensitive teeth which were anterior to the molars, demonstrated cervical erosion/abrasion or gingival recession, and for which a tactile hypersensitivity stimulus score of 10 to 50 grams of force (Yeaple probe) and an air blast stimulus score of 2 or 3 (Schiff Cold Air Sensitivity Scale) were presented at the baseline examination.
- Subjects needed to be available for the duration of the study, and to sign an informed consent form.
- Teeth that were abutments for partial dentures, and teeth exhibiting extensive or defective restorations, caries, fractures, excessive mobility, or suspected pulpal pathology were not included in the study.
- Subjects who had orthodontic appliances, more than one incisor with a prosthetic crown or veneer, tumors of the soft or hard oral tissues, moderate or advanced periodontal disease, or more than one carious lesion were excluded from the study.
- Subjects were also excluded from the study if they were concurrently using medications, including analgesics with a potential to mask pain sensation, or if they had used commercially available desensitizing agents within the three months prior to the study.
- Pregnant women and individuals who were participating in another clinical trial were also excluded.

Qualifying subjects were stratified according to baseline tactile and air blast sensitivity scores and were randomly assigned within strata to one of the following two study treatments: the new toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride, or Sensodyne Total Care F toothpaste. Both toothpastes were provided in original tubes, over-wrapped with

opaque white paper to ensure the double-blind design. Subjects were also given a soft bristle toothbrush, and instructed to brush their teeth twice a day (morning and evening) for one minute each time. A log of the dispensed products was kept, and all clinical supplies were refurbished as needed.

After the baseline evaluation, the subjects were re-evaluated at two, four, and eight weeks. At each time point, they received a thorough oral examination of their hard and soft tissues, followed by a careful evaluation of their dentin hypersensitivity using the Yeaple probe and the air/water syringe.

All examinations were performed by the same investigator throughout the study.

Tactile Sensitivity Assessment

This assessment was conducted using a calibrated Model 200A Yeaple Electronic Pressure Sensitive Probe (Yeaple Research, Pittsford, NY, USA). Scores were recorded in terms of a quantified, reproducible force (grams).[13-15] After presetting the initial force to 10 grams, the probe tip was passed over the exposed dentin on the buccal surface of the selected teeth, apical to the cemento-enamel junction. Subsequent passes were made, each time with the applied force increased by 10 grams until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams was reached. A force of 50 grams was considered the cut-off point; higher scores on this index correspond to lower levels of dentin hypersensitivity.

Air Blast Sensitivity Assessment

This assessment was conducted by directing a one-second blast of air onto the exposed buccal root surface of the sensitive tooth, from a distance of one centimeter using the air component of a dental air/water syringe. After shielding the adjacent proximal teeth from the air blast through the placement of two fingers, the air blast was applied with a pressure of 60 p.s.i. (± 5 p.s.i) and a temperature of 70°F (± 3°F) for one second.

Sensitivity was recorded in accordance with the air sensitivity scale described by Schiff, *et al.*[15] as follows:

0 = Tooth/Subject sensitivity does not respond to air stimulation;
1 = Tooth/Subject respond to air stimulus, but does not request discontinuation of stimulus;
2 = Tooth/Subject responds to air stimulus, and requests discontinuation or moves from stimulus;
3 = Tooth/Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus.

Only teeth with a score of 2 or 3 were selected at the baseline examination; the higher the score, the higher the sensitivity.

Statistical Methods

Statistical analyses were performed separately for the tactile sensitivity assessments and air blast sensitivity assessments, respectively. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using an independent t-test. Within-treatment comparisons of the baseline versus follow-up tactile sensitivity and air blast sensitivity scores were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted tactile sensitivity and air blast sensitivity scores at the follow-up examinations were performed using Analyses of Covariance (ANCOVA). All statistical tests of hypothesis were two-sided, and employed a level of significance of $\alpha = 0.05$.

Results

All eighty (80) subjects who were enrolled at baseline complied with the protocol and completed the eight-week clinical study. A summary of the baseline sensitivity data is presented in Table I. The treatment groups did not differ significantly with respect to either tactile or air blast scores at baseline.

Throughout the study, there were no adverse events on the soft or hard tissues of the oral cavity which were observed by the examiner, or reported by the subjects when questioned.

This double-blind clinical study provided an investigative comparison of the efficacy of two dentifrices with respect to the dentin hypersensitivity scores over an eight-week period.

After two, four, and eight weeks of dentifrice use (Tables II, IV, and VI), subjects assigned to the Test Dentifrice group (the

Table I
Summary of the Baseline Tactile and Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Parameter	Treatment	n	Sensitivity Scores (Mean ± SD)[3]
Tactile Sensitivity	Test Dentifrice[1]	40	12.13 ± 3.74
	Control Dentifrice[2]	40	13.63 ± 4.38
Air Blast Sensitivity	Test Dentifrice[1]	40	2.49 ± 0.37
	Control Dentifrice[2]	40	2.51 ± 0.40

[1]Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2]Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3]No statistically significant difference was indicated between the two treatment groups at baseline with respect to either mean tactile sensitivity or mean air blast sensitivity scores.

Table II
Summary of the Two-Week Baseline-Adjusted Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

		Baseline-adjusted Tactile Sensitivity Scores	Within Treatment Analysis		Between Treatment Comparison	
Treatment	n	(Mean ± SD)	Percent Change[3]	Sig.[4]	Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	40	26.45 ± 6.99	105.4%	$p < 0.05$	37.0%	$p < 0.05$
Control Dentifrice[2]	40	19.30 ± 6.99	49.8%	$p < 0.05$		

[1]Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2]Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3]Percent change exhibited by the two-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the two-week examination.
[4]Significance of paired t-test comparing the baseline and two-week examinations.
[5]Difference between two-week baseline-adjusted means expressed as a percentage of the two-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

Table III
Summary of the Two-Week Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	1.65 ± 0.51	34.0%	p < 0.05	23.9%	p < 0.05
Control Dentifrice[2]	40	2.17 ± 0.51	13.4%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the two-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the two-week examination.
[4] Significance of paired t-test comparing the baseline and two-week examinations.
[5] Difference between two-week baseline-adjusted means expressed as a percentage of the two-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Table IV
Summary of the Four-Week Baseline-Adjusted Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Tactile Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	40.98 ± 7.87	218.2%	p < 0.05	30.0%	p < 0.05
Control Dentifrice[2]	40	31.52 ± 7.87	144.7%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the four-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the four-week examination.
[4] Significance of paired t-test comparing the baseline and four-week examinations.
[5] Difference between four-week baseline-adjusted means expressed as a percentage of the four-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

new toothpaste with 8% arginine, calcium carbonate, and 1450 ppm fluoride) exhibited statistically significant improvements from baseline in baseline-adjusted mean tactile sensitivity scores of 105.4%, 218.2%, and 252.2%, respectively. Additionally, after two, four, and eight weeks of dentifrice use (Tables III, V, and VII), subjects assigned to the Test Dentifrice group exhibited statistically significant reductions from baseline in baseline-adjusted mean air blast sensitivity scores of 34.0%, 63.4%, and 80.5%, respectively.

After two, four, and eight weeks of dentifrice use (Tables II, IV, and VI), subjects assigned to the Control Dentifrice group (Sensodyne Total Care F) exhibited statistically significant improvements from baseline in baseline-adjusted mean tactile sensitivity scores of 49.8%, 144.7%, and 214.2%, respectively.

Table V
Summary of the Four-Week Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	0.92 ± 0.56	63.4%	p < 0.05	32.0%	p < 0.05
Control Dentifrice[2]	40	1.35 ± 0.56	46.1%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the four-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the four-week examination.
[4] Significance of paired t-test comparing the baseline and four-week examinations.
[5] Difference between four-week baseline-adjusted means expressed as a percentage of the four-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Table VI
Summary of the Eight-Week Baseline-Adjusted Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Tactile Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	45.40 ± 5.30	252.5%	p < 0.05	12.2%	p < 0.05
Control Dentifrice[2]	40	40.47 ± 5.30	214.2%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the eight-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the eight-week examination.
[4] Significance of paired t-test comparing the baseline and eight-week examinations.
[5] Difference between eight-week baseline-adjusted means expressed as a percentage of the eight-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Additionally, after two, four, and eight weeks of dentifrice use (Tables III, V, and VII), subjects assigned to the Control Dentifrice group exhibited statistically significant reductions from baseline in baseline-adjusted mean air blast sensitivity scores of 13.4%, 46.1%, and 72.5%, respectively.

Relative to the Control Dentifrice group, after two, four, and eight weeks of dentifrice use, the Test Dentifrice group exhibited statistically significant improvements in baseline-adjusted mean tactile sensitivity scores of 37.0%, 30.0%, and 12.2%, respectively. Relative to the Control Dentifrice group, after two, four, and eight weeks of dentifrice use, the Test Dentifrice group exhibited statistically significant reductions in baseline-adjusted mean air blast sensitivity scores of 23.9%, 32.0%, and 29.3%, respectively.

Table VII
Summary of the Eight-Week Baseline-Adjusted Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Baseline-adjusted Air Blast Sensitivity Scores (Mean ± SD)	Within Treatment Analysis: Percent Change[3]	Within Treatment Analysis: Sig.[4]	Between Treatment Comparison: Percent Difference[5]	Between Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	0.49 ± 0.39	80.5%	$p < 0.05$	29.3%	$p < 0.05$
Control Dentifrice[2]	40	0.69 ± 0.39	72.5%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care F toothpaste containing 2% potassium ion as 3.75%, potassium chloride, and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the eight-week baseline-adjusted mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the eight-week examination.
[4] Significance of paired t-test comparing the baseline and eight-week examinations.
[5] Difference between eight-week baseline-adjusted means expressed as a percentage of the eight-week baseline-adjusted mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Discussion

Dentin hypersensitivity is a significant problem and a "quality of life" concern for many individuals. It is characterized by a sharp, transient pain which occurs in response to a sensory stimulus that affects eating, drinking, brushing teeth, and breathing.[16] This painful condition affects nearly 40 million Americans,[17] and can be seen in all age groups.[18] Epidemiology research suggests that prevalence peaks between 30 and 40 years of age, and that women experience a higher incidence of dentin hypersensitivity at a younger age than men.[18] Patients who have received periodontal therapy are four times more likely to develop hypersensitivity then the general population.[19] This is because gingival recession and exposed root surfaces occur as a result of periodontal disease and its associated therapy. The cementum on these exposed roots is partially or totally removed during scaling and root planing, with the result that the dentin tubules are exposed to the oral environment. Any change in fluid pressure within the tubule is detected by the odontoblast, the nerve becomes polarized, and the patient feels pain.

The treatment choices available to relieve dentin hypersensitivity are to occlude the dentin tubules or to desensitize the nerves so that they are not responsive to stimulation. Potassium salts have been added to dentifrices as sensitivity-reducing agents for many years. A number of clinical studies have demonstrated that toothpastes containing 2% potassium ion, as potassium nitrate, potassium citrate, and potassium chloride, are more effective in reducing dentin hypersensitivity than a regular fluoride toothpaste,[20] yet the detailed mechanism of action of potassium ions is not fully elucidated. It is believed that delivering and maintaining a high concentration of extracellular potassium ion deep in the dentin tubules and around the nerve endings causes depolarization of nerve fiber membranes and prevents repolarization.[9]

A second route that has been investigated by the dental research community is to occlude dentin tubules or reduce their diameter with a technology that coats the dentin surface and blocks the tubules, such as a varnish or material which precipitates *in situ*, such as calcium phosphate.[21] This approach impairs or limits the displacement of fluids in the dentin tubule, *i.e.*, hydrodynamic flow and the blockage of painful stimuli. While several *in vitro* studies have shown occlusion of dentinal tubules with calcium phosphate,[21-24] there is a paucity of clinical data proving efficacy *in vivo*.

An essential amino acid, arginine, first isolated from a lupin seedling extract in 1886 by the Swiss chemist Ernst Schultze, has been investigated in combination with bicarbonate and calcium carbonate for its ability to occlude dentin tubules and reduce pain from dentin hypersensitivity.[10] This technology has recently been further developed and formulated into a toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate.[20]

The results of the present clinical investigation confirm the results of a previous study conducted in Canada.[12] It shows that a new toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate, and Sensodyne Total Care F toothpaste, containing 2% potassium ion as potassium chloride, both provide significant reductions in dentin hypersensitivity when used twice daily for a period of eight weeks. More importantly, this double-blind clinical study clearly shows that this new arginine toothpaste provides significantly superior control of dentin hypersensitivity ($p < 0.05$) compared to Sensodyne Total Care F toothpaste, after two, four and eight weeks of use.

The clinical results reported in this study, together with the results of the study conducted in Canada and reported in the previous paper in this issue,[12] confirm the superior efficacy of a new toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride in treating dentin hypersensitivity compared to Sensodyne Total Care F toothpaste.

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A Breakthrough Therapy for Dentin Hypersensitivity: How Dental Products Containing 8% Arginine and Calcium Carbonate Work to Deliver Effective Relief of Sensitive Teeth

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Abstract

- **Objective:** These studies have utilized a range of state-of-the-art surface techniques to gain insight into the mechanism of action of a new technology for dentin hypersensitivity relief based upon arginine and calcium carbonate and, in particular, to address important questions regarding the nature and extent of dentin tubule occlusion.
- **Methods:** Confocal laser scanning microscopy (CLSM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) have been used to assess tubule occlusion. Energy dispersive x-ray (EDX) and electron spectroscopy for chemical analysis (ESCA) have been used to identify the composition of the dentin plug. CLSM has also been used to compare the mechanism of action of the toothpaste and the desensitizing prophylaxis paste, to address whether both the arginine and the calcium carbonate components are essential to occlusion, to identify the location of the arginine within the occluded dentin, and to demonstrate resistance of the occlusion to acid challenge. Hydraulic conductance has been used to assess the effectiveness of the arginine-calcium carbonate technology in arresting dentin fluid movement, to evaluate the effects of pulpal pressure on the robustness of the occlusion, and to confirm the resistance of the occlusion to an acid challenge.
- **Results:** The CLSM, SEM, and AFM studies demonstrate that the arginine-calcium carbonate technology is highly effective in rapidly and completely occluding dentin tubules. The EDX and ESCA studies show that the dentin surface deposit and occluded tubule plug contain high levels of calcium and phosphate, as well as carbonate. CLSM has confirmed that the toothpaste and the desensitizing prophylaxis paste have the same mechanism of action, that the arginine and calcium carbonate components are both essential to the effectiveness of these products, and that the arginine becomes incorporated into the dentin plug. The hydraulic conductance studies demonstrate that the occlusion provided by the arginine-calcium carbonate technology results in highly significant reductions in dentin fluid flow, and that the tubule plug is resistant to normal pulpal pressure and acid challenge.
- **Conclusion:** A breakthrough technology based upon arginine and calcium carbonate provides clinically proven benefits with respect to rapid and lasting relief of dentin hypersensitivity. It is unique in that two of its key components, arginine and calcium, are found naturally in saliva, and that the arginine and calcium carbonate work together to accelerate the natural mechanisms of occlusion to deposit a dentin-like mineral, containing calcium and phosphate, within the dentin tubules and in a protective layer on the dentin surface.

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Introduction

Dental pain is a commonly experienced problem and a major reason why patients visit the dentist. There are several causes of dental pain. Pain arising from the tooth occurs because the dental pulp and associated nerves become exposed to the external oral environment. Such pain may be derived from dental disease, such as a cavity, or from physical trauma, such as a broken tooth.[1] Dentin hypersensitivity is an acute pain condition that typically occurs when the surface of the root becomes exposed through recession of the gingiva.[2,3] Gingival recession may occur naturally, but it is more often caused by over-aggressive tooth brushing or periodontal disease. Just as enamel protects the underlying coronal dentin from external stimuli, so the gingiva protects the underlying cementum and root dentin. Once the gingiva has receded, cementum can readily be removed, and dentin tubules can become exposed and opened, resulting in a conduit that can transmit external stimuli to the nerves.

It is commonly accepted that the hydrodynamic theory best explains the mechanism of dentin hypersensitivity.[4-6] Stimuli, such as heat, cold, evaporation, and osmotic and pressure changes cause fluid movement within the tubules, inducing sharp pain responses in the nerve fibers.[7] Pain due to dentin hypersensitivity is generally transient in nature, occurring instantaneously after a stimulus, and diminishing rapidly thereafter.[8-10] Identifying the true source of pain is critical to effective treatment and management of pain.[1, 8-11]

There are two primary approaches to treating sensitive teeth. One is to interfere with nerve transmission, and potassium salts are commonly used to achieve this end.[8-10] It is believed that potassium depolarizes the nerve fibers and this, subsequently, interferes with the transmission of the pain response. Most over-the-counter toothpastes for relief of dentin hypersensitivity are formulated with a potassium salt. To be effective, the potassium ions must diffuse through the dentin tubules against a positive flow of dentin fluid, and must build up and be maintained

at elevated concentrations in order for the nerve fibers to remain in a depolarized state. This build-up takes time; typically, it is necessary to brush twice daily for at least two weeks to see reductions in dentin hypersensitivity, and for four to eight weeks to demonstrate significant relief as compared to regular fluoride toothpaste.[10]

Occluding dentin tubules is the second means of treating dentin hypersensitivity. In this approach, fluid within the tubule is isolated from external stimuli, resulting in an absence of fluid movement to trigger a pain response.[8-10] There are many means of occluding dentin tubules, ranging from invasive techniques, such as laser etching of the dentin surface,[12] to noninvasive methods, such as the application of a gel or toothpaste containing an occluding agent.[13] A few marketed toothpastes contain an occluding agent, specifically one of either a strontium or stannous salt. Typically, these formulations have been shown to provide reductions in dentin hypersensitivity after four weeks of twice daily use.[10,14,15] Both strontium and stannous salts work by precipitating insoluble metal compounds on the dentin surface, thereby occluding or partially occluding open dentin tubules.[14,15] Strontium salts have the disadvantage of incompatibility with fluoride, so they are generally not suitable for a daily use toothpaste. Stannous salts have traditionally been associated with poor taste and staining.[10]

An ideal dentin hypersensitivity treatment would mimic the natural desensitizing process, inducing changes in dentin that lead to rapid and lasting occlusion of dentin tubules.[16] Further, the treatment would be easy to apply, and would have no side effects. Most of the current technologies that deliver rapid occlusion are only available as professionally applied, in-office products.[7] Until now, there has been no toothpaste technology that provides rapid and lasting relief of sensitivity without any adverse effects, such as fluoride incompatibility, poor taste, or staining.[10]

A breakthrough technology, based upon arginine and calcium carbonate, has been developed and validated for treating sensitive teeth.[10] This technology is unusual in that it can be delivered as a conventional daily-use toothpaste with fluoride, as well as a professionally applied desensitizing treatment for use during periodic prophylaxis procedures. A dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride has been clinically proven to provide superior relief of dentin hypersensitivity compared to a leading toothpaste containing 2% potassium ion as the active agent.[17,18] In addition, a desensitizing prophylaxis paste with 8% arginine, calcium carbonate, and prophylaxis-grade silica has been clinically proven to provide instant and lasting relief following a single professional application.[19,20] Both products work by effectively plugging and sealing dentin tubules. In contrast to other products which occlude dentin tubules, this breakthrough technology is unique in that: 1) two of its key components, arginine and calcium, are found naturally in saliva; and 2) the arginine and calcium carbonate work together to accelerate the natural mechanisms of occlusion by depositing a dentin-like mineral, containing calcium and phosphate, within the dentin tubules and in a protective layer on the dentin surface.

This paper provides new insights regarding the mechanism of action of this novel arginine-calcium carbonate technology. State-of-the-art surface techniques have been used to address important questions regarding the nature and extent of occlusion. Confocal laser scanning microscopy (CLSM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) have been used to assess the effectiveness of tubule occlusion in terms of surface coverage and depth of tubule penetration. Energy dispersive x-ray (EDX) and electron spectroscopy for chemical analysis (ESCA) have been used to identify the composition of the dentin plug. CLSM has also been used to compare the mechanism of action of the toothpaste and the desensitizing prophylaxis paste, to address whether both the arginine and the calcium carbonate components are essential to bringing about occlusion, to identify the location of the arginine within the occluded dentin, and to demonstrate the resistance of the occlusion to an acid challenge. Finally, hydraulic conductance has been used to assess whether the occlusion achieved with the arginine-calcium carbonate technology is effective in arresting fluid movement within the dentin tubules, to evaluate the effects of pulpal pressure on the robustness of the occlusion, and to confirm the resistance of the occlusion to acid challenge.

Materials and Methods

Preparation of Dentin Specimens for All Surface Analysis Experiments

Dentin slices, approximately 800 microns in thickness, were cut from the crown section of human molars in a parallel manner, slightly below the enamel-dentin junction, using a water-cooled, diamond-bladed saw. Typically, two to five useable specimens were obtained from each tooth. The dentin slices were then polished on one side using 600 grit wet paper and a polishing wheel to create an even and uniform surface. The specimens were further polished by using a polishing cloth (Microcloth®, Buehler, Lake Bluff, IL, USA), which was wetted with a five-micron alumina slurry.

The side that was polished magnified printed text when the specimen was placed over it. Each specimen was polished for approximately 30 seconds to make each specimen shiny. The dentin slices were then examined under a microscope to confirm that the surface was uniformly polished. The polished specimens were then placed in a jar of deionized water, and sonicated for 10 minutes to remove the polishing abrasive. After sonication, the specimens were rinsed with water.

The tubules were opened by etching the dentin specimens in a Petri dish with a 1% citric acid solution, using mild back-and-forth agitation for 20 seconds. After etching, the specimens were rinsed with deionized water, and then placed in a jar of deionized water and sonicated once again for 10 minutes. The etched and sonicated specimens were stored in a phosphate buffer saline (PBS, pH = 7).

Selection of Dentin Specimens for All Surface Analysis Experiments

CLSM was used to inspect the dentin specimens to ensure that the tubules were open and the surface was uniform and free of debris, *i.e.*, the specimens were of sufficient quality to be used for further experiments. The confocal laser scanning microscope was operated in reflectance mode using the 488 nm laser line. A 50× material science dry lens was used to view the specimens with a 4× zoom.

Treatment of Specimens Without Use of Mechanical Action

Dentin specimens prepared as described above were placed on a microscope slide with the polished side up. A piece of double-sided tape was used to hold the dentin sample to the microscope slide The sample was wetted with PBS buffer, then test product was applied to the dentin surface, mixed with the PBS, and spread across the entire surface using gentle strokes and a camel hair brush. The samples were left undisturbed for 15 minutes at room temperature. After this, the samples were placed in a jar containing 30 ml of PBS buffer, where they remained for 15 minutes while stirring. The samples were then gently rinsed to ensure removal of any excess product from the surface, and dried prior to analysis.

Treatment of Specimens Using Mechanical Action

Dentin specimens prepared as described above were placed on a microscope slide with the polished side up. A piece of double-sided tape was used to hold the dentin sample to the microscope slide. The sample was wetted with PBS buffer, then the test product was applied to the dentin surface. A small brush was used to brush the entire surface of the dentin for one minute. After this, the samples were place in a jar containing 30 ml of PBS buffer and a stir bar, where the samples were allowed to sit in the buffer; they remained for fifteen minutes while stirring. The samples were then gently rinsed to ensure removal of any excess product from the surface. The procedure was repeated for a dentin specimen without the use of a product, with the use of a brush only, as a negative control. The samples were dried prior to analysis by CLSM.

Test Products

Three different products containing 8% arginine were evaluated. One was a calcium carbonate-based toothpaste with 8% arginine and 1450 ppm fluoride as sodium monofluorophosphate (SMFP), the second was a dicalcium phosphate dihydrate toothpaste containing 8% arginine and 1450 ppm fluoride as SMFP, and the third was a desensitizing prophylaxis paste (marketed in the United States as ProClude, Ortek Therapeutics, Roslyn Heights, NY, USA) with 8% arginine, a calcium carbonate base, and prophylaxis-grade silica. Control products, without arginine and/or calcium carbonate, were also used in some experiments.

Evaluation of Dentin Occlusion and Analysis of the Composition of the Dentin Plug

Dentin specimens before and after treatment with the desensitizing prophylaxis paste were examined by SEM. Five dentin disks were prepared. Prior to treatment, the dentin disks were examined by low energy SEM, to ensure that the dentin tubules were in an open unoccluded state. Each sample served as its own baseline. Within the confines of this particular experiment, the dentin disks were treated five times using the procedure without the mechanical action described above. The samples were then examined a second time by low voltage SEM to determine the effect of the arginine-calcium carbonate paste on dentin tubule occlusion. After evaluation of tubule occlusion by SEM, samples were studied by ESCA to quantitatively determine the elemental composition of the surface, or by EDX analysis to qualitatively determine the elemental composition of the occluding material. This analysis was performed on the occluded and a freeze-fractured face of some of the treated dentin disks.

Confirmation of Dentin Occlusion and Assessment of the Formation of a Protective Layer

AFM was used to view the surface of dentin samples with open tubules, and those that had been occluded by treatment five times with the desensitizing prophylaxis paste. Prior to AFM analysis, the dentin disks were washed with deionized water and dried under nitrogen gas. Samples were imaged dry using a Nanoscope V Dimension 3100/5000 AFM (Veeco, Santa Barbara, CA, USA). Images were captured in the tapping mode with Veeco FESP/RFESP cantilevers. All images were amplitude images with pixel resolution between 1024×1024 and 2048×2048, and were scanned at 0.4 Hz for 5×5 micron images and 0.2 Hz for 10×10 micron images.

The Extent of Dentin Occlusion and Resistance to Acid Challenge

A Leica TCS SP (Leica, Wetzlar, Germany) confocal laser scanning microscope, equipped with a spectral detection system, was used to visualize the dentin occlusion and the effect of an acid challenge. The 488 nm line from the argon laser, along with a PLO APO 50x objective, was used in all experiments.

Dentin specimens were occluded without mechanical action as described above. Five applications of arginine-calcium carbonate desensitizing paste were used to ensure complete occlusion. CLSM was used to visualize changes in the occluded surface both from XY (top) and XZ (side) perspectives after exposure of the occluded dentin specimens to cola. The specimens were exposed to acidic conditions simulating consumption of an acidic beverage by immersing the specimens in 10 ml of cola in a small Petri dish with mild agitation for one minute. After one minute, the samples were rinsed with deionized water and viewed by CLSM. This procedure was repeated to examine the effects of two acid challenges.

Location of Arginine in the Dentin

Dye-binding experiments were conducted to determine if arginine could be detected in the dentin tubules by using 5(6) fluorescein isothiocyanate mixed isomer dye (FITC). FITC is specific for amino groups. Dentin specimens occluded by treating with the arginine-calcium carbonate desensitizing paste were immersed in FITC dye and viewed by CLSM in the fluorescence and reflectance mode. An untreated dentin specimen with open tubules was used as a control.

The Effects of Occlusion on Dentin Fluid Flow

Human molars were sectioned, mounted as dentin segments, etched, and connected to a Flodec device (de Marco Engineering, Geneva, Switzerland) for hydraulic conductance measurements using the method of Pashley and coworkers.[22] The hydraulic conductance of each segment after etching was measured at 70 cm water pressure. This measurement represented the baseline etched value. Each segment was brushed for one minute with 50 g

application force using a soft bristle toothbrush loaded with the arginine-calcium carbonate toothpaste with fluoride. Segments were rinsed with deionized water, and incubated in PBS for at least two hours with agitation. The segments were then rinsed again with deionized water, connected to the Flodec apparatus, and the conductance measured at 70 cm water pressure. This process was carried out a total of 14 times to demonstrate the sequential effects of multiple product treatments.

To determine the longevity and reactivity of the occlusive deposits, segments were then incubated in PBS with agitation for seven days, followed by conductance measurements. To determine longevity under pulpal pressure, segments were next connected to pulpal PBS pressure (20 cm water, 0.28 psi) with PBS incubation for seven days. Conductance measurements were taken again.

Results

Confocal Laser Scanning Microscopy

CLSM was used to compare dentin specimens treated with: a) a control toothpaste containing calcium carbonate (pH = 9); b) an 8% arginine-calcium carbonate toothpaste with 1450 ppm fluoride as MFP (pH = 9); c) an 8% arginine-dical toothpaste with 1450 ppm fluoride as MFP (pH = 7); and d) an 8% arginine-calcium carbonate desensitizing paste with high cleaning silica (pH = 9). The results are shown in Figure 1.

The results from the study showed that dentin specimens treated with either the 8% arginine-calcium carbonate toothpaste or the 8% arginine-calcium carbonate desensitizing prophylaxis paste were completely occluded within five applications without brushing or mechanical force. This indicates that these two arginine-calcium carbonate pastes behave similarly, and that the presence of fluoride has no impact on dentin occlusion. In contrast, no dentin occlusion was observed with the calcium carbonate control toothpaste, without fluoride or arginine, nor was any occlusion observed with the 8% arginine-dical control paste which has a neutral pH, whereas the calcium carbonate formulations have an alkaline pH of 9. These results demonstrate that the arginine-calcium carbonate technology is highly effective in occluding open dentin tubules. They also demonstrate that this technology works effectively when delivered from a fluoride toothpaste and from a silica-containing prophylaxis paste.

Scanning Electron Microscopy

SEM was used to obtain high resolution images of dentin treated with the 8% arginine-calcium carbonate desensitizing prophylaxis paste. The specimens were also freeze-fractured to enable observation of the occlusion as a function of depth, and to allow characterization of the material coating the surface and filling the dentin tubules by EDX. The SEM images are shown in Figure 2, and the freeze-fractured images with the EDX analysis are shown in Figure 3

The SEM analysis shows that treatment with the prophylaxis paste containing 8% arginine and calcium carbonate was highly effective in occluding dentin tubules, confirming the results of the CLSM. The freeze-fracture SEM of one of the plugs showed that it penetrated below the dentin surface. Chemical mapping showed that the surface layer on the dentin consisted mainly of calcium and phosphate. Within the tubules, calcium and phosphate were also found along with silica.

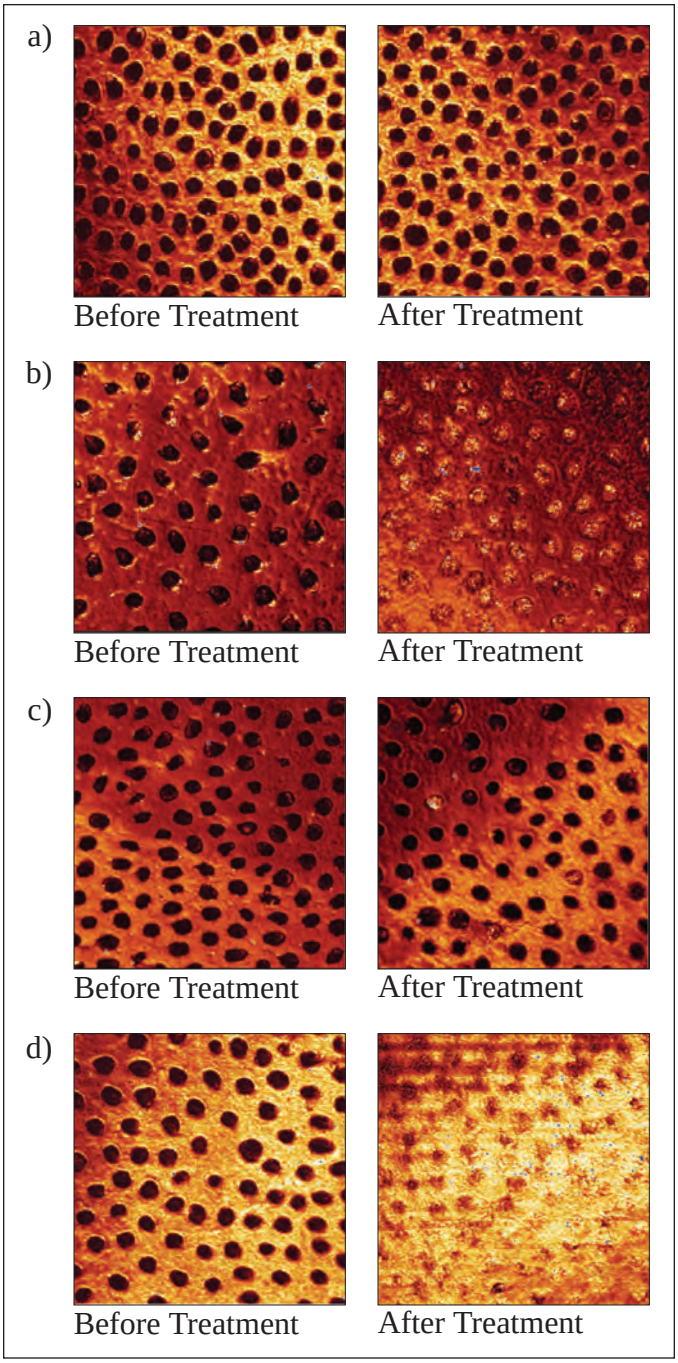

Figure 1. *Dentin specimens before and after treatment with: a) $CaCO_3$ toothpaste without fluoride or arginine; b) calcium carbonate toothpaste with 8% arginine and 1450 ppm MFP; c) dical toothpaste with 8% arginine and 1450 ppm MFP; and d) desensitizing prophylaxis paste with 8% arginine and calcium carbonate.*

Atomic Force Microscopy

AFM was used to evaluate dentin surfaces after treatment with the prophylaxis paste containing 8% arginine and calcium carbonate. An untreated dentin specimen was used as a control. AFM images of the untreated dentin specimens at various magnifications are shown in Figure 4. Figure 5 shows the AFM images after treatment.

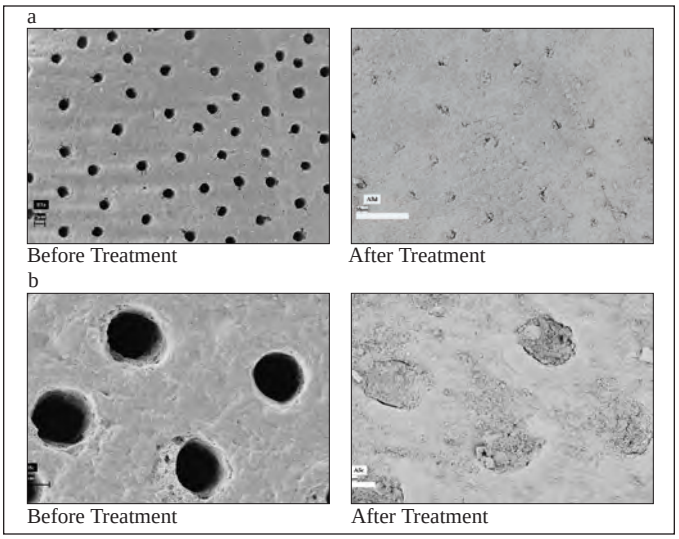

Figure 2. *Scanning electron micrographs of dentin surfaces before and after treatment with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate. a) 2000× magnification and b) 10,000× magnification.*

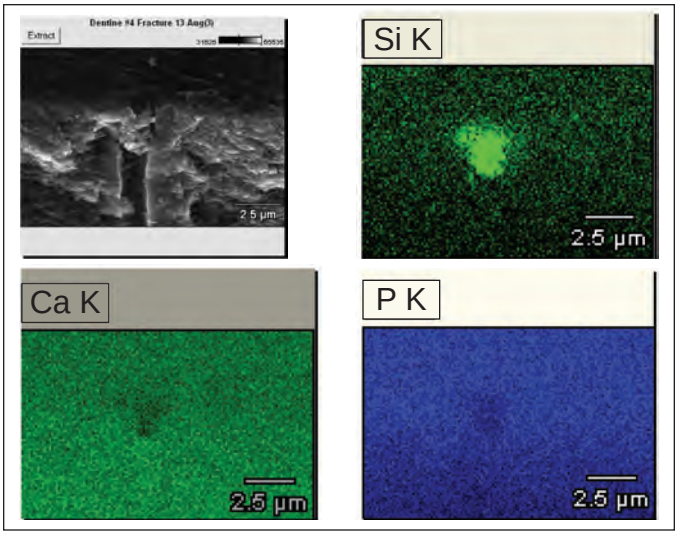

Figure 3. *Scanning electron micrographs of freeze-fractured dentin surfaces after treatment with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate. Left figure illustrates SEM freeze-fracture and right illustrates EDX chemical mapping.*

The AFM images of untreated dentin show that the tubules were completely open. Zooming in on a single tubule reveals helical fine structure on the dentin surface. The AFM images of a treated specimen show that the helical structure on the surface was no longer present as a result of formation of a protective layer, and the tubules were sealed shut. These results also confirm that the arginine-calcium carbonate technology is highly effective in occluding dentin tubules. In addition, they demonstrate that it is also effective in providing a protective coating across the intact dentin surface between the tubules.

Effect of Mechanical Action on the Action of Arginine-Calcium Carbonate

A study was conducted to assess the effects of application of the 8% arginine-calcium carbonate toothpaste directly to the dentin surface by working in the product with a small brush or foam swab. The product was applied by brushing the dentin surface for one minute, followed by incubation in PBS buffer for 15 minutes. As a control, a dentin specimen was brushed for one minute without product, and then incubated in PBS buffer for 15 minutes. The surface was examined before and after treatment by CLSM. The results are shown in Figure 6.

The results of this study show that brushing the dentin surface alone for one minute had no effect in occluding dentin tubules. When the arginine-calcium carbonate toothpaste was applied for one minute with a brush, complete occlusion was observed after just one application, demonstrating that brushing accelerates the occlusion process.

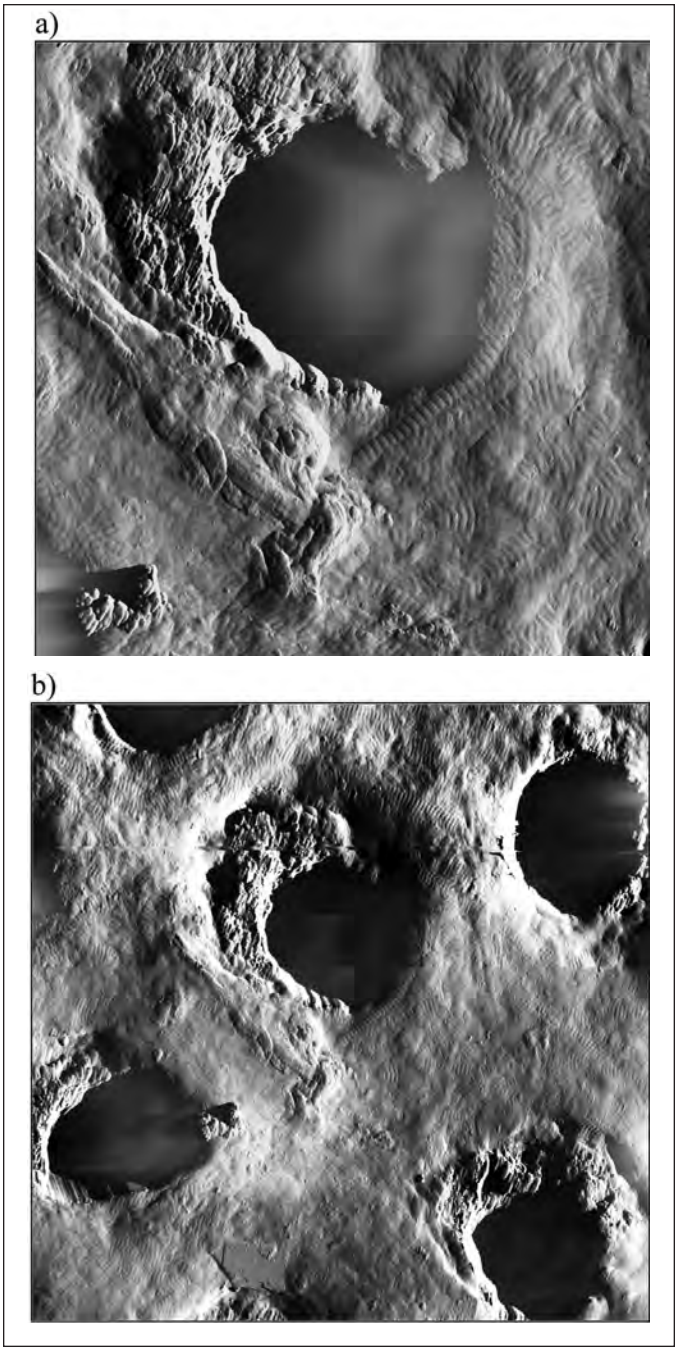

Figure 4. *Atomic force microscope images of untreated dentin. a) a single tubule and b) multiple tubules.*

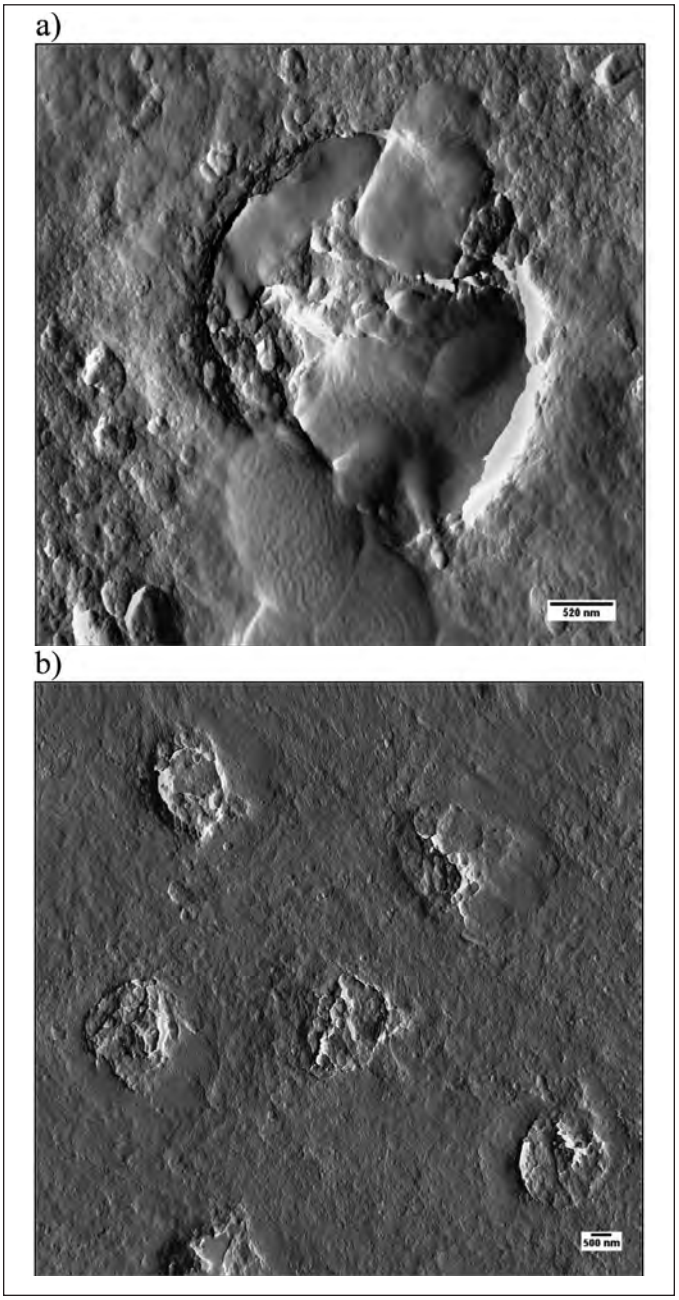

Figure 5. *Atomic force microscope images of dentin treated with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate. a) a single tubule and b) multiple tubules.*

Confocal Laser Scanning Microscopy and Dye Binding Experiments

Dentin specimens that were treated with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate were examined by CLSM in the fluorescence mode and reflectance mode. FITC dye, which is specific for amino groups, was used to stain the dentin samples. The reflectance mode was used to disclose solid surfaces. A dentin specimen that was untreated was used as a control. The specimens were viewed in both the XY and XZ mode. Figure 7 shows the results of the dye binding experiments.

Both fluorescence and reflectance mode images showed that untreated dentin specimens contained tubules that were completely open. For the specimens treated with the 8% arginine-calcium carbonate desensitizing prophylaxis paste, the reflectance mode view in the XY orientation shows that the tubules were completely occluded. The XZ view confirms this. In the fluorescence mode, the fluorescence signal from the FITC dye was concentrated in the area where the tubules were present. The XZ view indicates that the dye has penetrated into the dentin tubule and is located within the solid plug. Thus, these results support that the role of arginine is to direct the calcium carbonate into the open dentin tubule, where it becomes incorporated into the dentin plug.

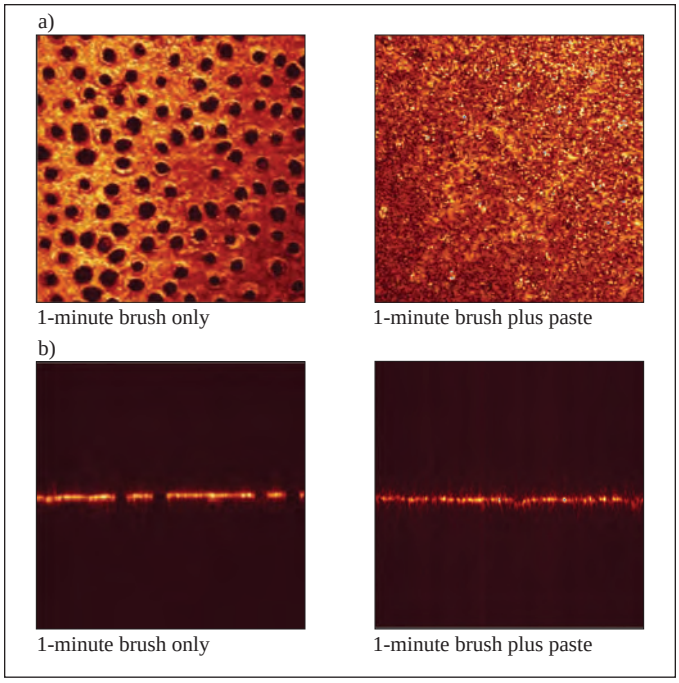

Figure 6. *Confocal microscopy analysis of dentin surfaces treated with the 8% arginine-calcium carbonate toothpaste. a) XY view and b) XZ view.*

Acid Resistance of Occluded Tubules

In order to determine whether or not the dentin tubules remained plugged after exposure to acidic beverages, dentin samples that were occluded with the 8% arginine-calcium carbonate desensitizing prophylaxis paste were exposed to cola for a total of two minutes to simulate consumption of an acidic beverage. The integrity of the dentin surface and the occluded dentin tubules was examined before and after exposure to cola by CLSM. Figure 8 shows the results of the CLSM analysis.

The CLSM of the occluded dentin samples shows that the tubules remain occluded after a total of two minutes' exposure to cola. This result demonstrates that the occluding layer is resistant to an acid challenge from a typical beverage that may be consumed following use of the product.

Chemical Analysis of Dentin Surface Before and After Treatment

ESCA was conducted on dentin samples before and after treatment with the 8% arginine-calcium carbonate desensitizing prophylaxis paste to characterize the chemical composition of the surface. The results are shown in Table I.

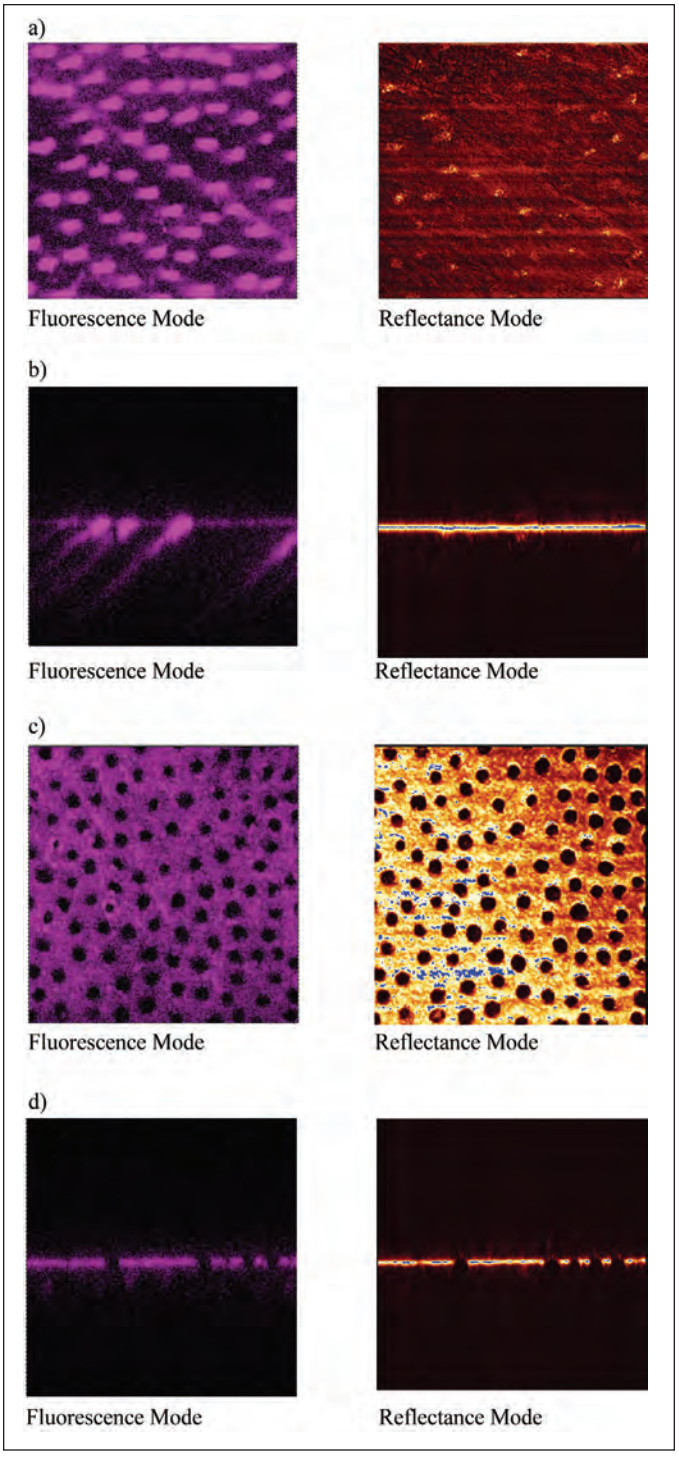

Figure 7. *Confocal images of dentin treated with the desensitizing prophylaxis paste with 8% arginine and calcium carbonate and untreated dentin in the fluorescence mode. a) treated XY view, b) treated XZ view, c) untreated XY view, and d) untreated XZ view.*

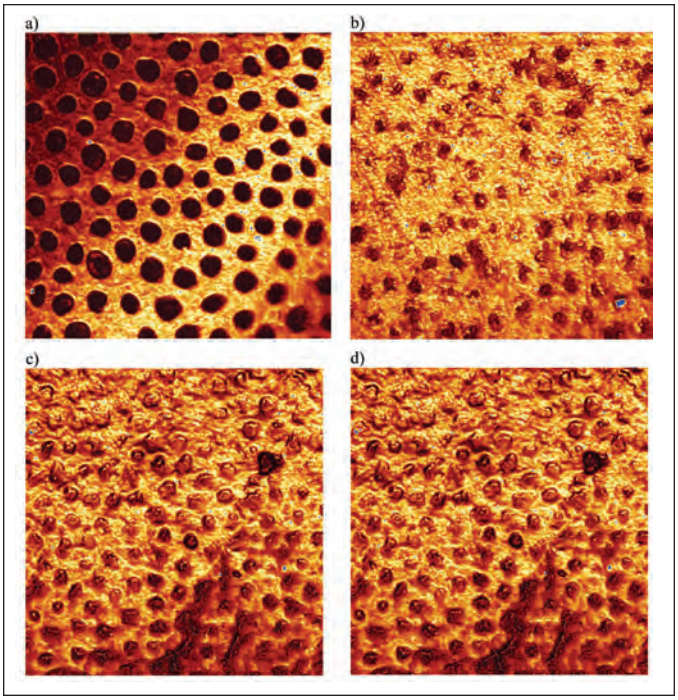

Figure 8. *Confocal images of a) untreated dentin, b) dentin treated with the prophylaxis paste with 8% arginine and calcium carbonate, c) treated dentin after one-minute exposure to cola, and d) treated dentin after two minutes total exposure to cola.*

The ESCA image of the dentin surface before treatment shows high levels of carbon, oxygen, and nitrogen. The levels of calcium and phosphorus are significantly lower. This result is consistent with the fact that the dentin surface is demineralized and the collagen matrix is exposed. No carbon in the form of carbonate was detected on the surface. Treatment with the 8% arginine-calcium carbonate desensitizing prophylaxis paste resulted in a dramatically different surface composition. Levels of carbon and nitrogen significantly dropped, and carbon associated with carbonate was detected. Calcium, oxygen, and phosphorus levels significantly increased, which is consistent with remineralization of the surface of the dentin and occlusion of the dentin tubules by a dentin-like mineral containing calcium and phosphate, as well as some calcium carbonate. The levels of silica also increased slightly, but the levels were small relative to the other chemical constituents of the dentin surface.

Hydraulic Conductance

Hydraulic conductance experiments were conducted to determine whether treatment of the dentin surface with the 8% arginine-calcium carbonate toothpaste effectively blocks fluid movement within the tubules. The results of the conductance experiments are summarized in Table II.

Table I
ESCA Analysis of Dentin Samples Before and After Treatment With the 8% Arginine-Calcium Carbonate Prophylaxis Paste

	Atomic Percent									
Dentin	C_{Total}	C_{CO3}	O	N	Ca	P	Na	F	Si	Ca/P
Untreated	59.35 ± 1.57	—	22.99 ± 1.45	15.07 ± 0.81	1.06 ± 0.49	0.87 ± 0.39	0.37 ± 0.05	—	0.28 ± 0.11	1.21
Treated	30.26 ± 5.13	1.51 ± 0.39	45.33 ± 3.36	2.33 ± 0.70	11.50 ± 1.08	8.39 ± 1.10	1.15 ± 0.28	—	0.99 ± 0.22	1.37

Table II
Hydraulic Conductance of Dentin Disks Treated With an 8% Arginine-Calcium Carbonate Toothpaste Containing 1450 ppm Fluoride as MFP

Treatment	% Reduction in Conductance*	Standard Deviation
1	63.41	12.09
2	57.43	10.04
3	63.34	8.79
4	69.70	15.33
5	79.56	14.67
6	81.74	15.25
7	78.83	9.65
8	79.67	8.35
9	83.10	9.60
10	80.55	7.62
11	92.66	0.85
12	92.02	2.39
13	84.43	8.26
14	81.56	2.95
7 Days in PBS	70.93	9.91
7-Day Pressure	79.46	7.52
Acid Challenge	77.25	10.43

* Relative to baseline.

The hydraulic conductance experiments show that the permeability of the dentin dropped by 63% after just one treatment. After 14 treatments, the permeability decreased to 82% of the baseline level. Incubation of the dentin specimens in PBS buffer for seven days showed that the permeability of the dentin was still significantly reduced by 71% relative to baseline. In addition, incubation under pressure for a further seven days resulted in a permeability reduction of 79% relative to baseline, indicating that the blocked tubules were resistant to typical dentin fluid pressures. Challenging the dentin specimen with 6% citric acid for three minutes showed that the permeability of the dentin remained reduced by 77% relative to baseline, further demonstrating that the plug is resistant to acid challenge

Discussion

Clinical studies have demonstrated that a toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride, as MFP, provides rapid and lasting reductions in dentin hypersensitivity and superior sensitivity relief to a market-leading toothpaste containing 2% potassium ion.[17,18] Clinical studies have also shown that an 8% arginine-calcium carbonate desensitizing prophylaxis paste provides instant relief when burnished directly onto a site that is sensitive, and that the sensitivity relief experienced following this single application is long-lasting.[19,20]

This paper reports the results of a series of experiments conducted to gain new insight on the mechanism of action of the arginine-calcium carbonate technology in providing sensitivity relief. In early research studies, Kleinberg proposed that the combination of arginine and calcium carbonate acts by forming a plug that occludes the dentin tubules. He suggested that the positively charged arginine is attracted to the negatively charged dentin surface where it helps attract and adhere calcium carbonate to the dentin surface and deep into the tubules. The association of the arginine and calcium carbonate *in situ* provides an alkaline environment which encourages endogenous calcium and phosphate ions to deposit and further plug and occlude the dentin tubules.[21]

Visualization of the dentin surface by CLSM, SEM, and AFM has clearly shown that the combination of arginine plus calcium carbonate is highly effective in occluding open dentin tubules. The combination of arginine, calcium, and alkaline pH appear to be key components in determining that effective occlusion occurs. No occlusion was observed when a calcium carbonate (alkaline pH) control dentifrice without arginine was applied to the dentin surface. This observation supports the hypothesis that arginine facilitates the adherence of calcium carbonate to the surface. When arginine was delivered in a neutral pH dentifrice containing dical as the source of calcium, no occlusion was observed. This result indicates that the presence of arginine and calcium alone, in the absence of alkalinity, is insufficient to create conditions that favor deposition of an arginine-calcium agglomerate on the dentin surface or within the dentin tubules. Calcium carbonate appears to be the preferred source of calcium because of its more alkaline pH.

Untreated dentin, etched with acid to open the tubules, has been shown by ESCA to have high levels of carbon, nitrogen, and oxygen in the dentin surface. The levels of calcium and phosphate were shown to be low, indicating that the surface was substantially demineralized and primarily composed of the supporting collagen matrix. Examination of the untreated dentin surface by AFM showed helical structures at the dentin surface, and this provides further evidence that the surface contains significant amounts of collagen. Treatment of the dentin surface with the 8% arginine-calcium carbonate desensitizing prophylaxis paste resulted in complete occlusion of the dentin tubules as demonstrated by SEM and AFM. The fine structure attributed to the collagen was no longer visible. Chemical analysis of the dentin surface using ESCA showed that the levels of calcium and phosphate had increased dramatically, and that this was accompanied by a decrease in carbon and nitrogen. Carbonate was also detected on the dentin surface after treatment. These results provide evidence that the treated surface has remineralized, and that some calcium carbonate has simultaneously deposited on the surface. ESCA is not able to distinguish nitrogen in the dentin surface derived from arginine from that derived from the collagen. EDX analysis of the dentin surface confirmed the results of the ESCA experiment in a more qualitative way. From the freeze-fracture specimens, silica was also detected within the tubule. It is likely that small particles of silica from the prophylaxis product entered the tubules and were sealed into the tubules along with arginine, calcium, carbonate, and phosphate. Very little silica was detected on the surface of the dentin.

Dye binding experiments using CLSM in both the fluorescence and reflectance mode using the amine-specific dye FITC provided evidence that arginine was present in the dentin tubules integral with the other components of the solid plug. In more detail, the dye binding experiments showed in reflectance mode, which detects reflections from the solid surfaces, that the dentin was completely occluded. In fluorescence mode, the fluorescence from FITC was highly concentrated within the occluded tubules. No dye was observed in the unoccluded tubules. As arginine has amine groups that bind to FITC, these results provide evidence

that arginine is present in the tubules along with a solid substance. This result, coupled with the demonstration of the presence of both calcium and carbonate in the dentin tubules, provides further evidence that arginine helps attract and bind calcium carbonate to the dentin surface and within dentin tubules.

The visualization of the occlusion by SEM, CLSM, and AFM provide strong evidence for the ability of products containing 8% arginine and calcium carbonate to occlude dentin. These techniques, however, do not establish whether this occlusion inhibits the movement of fluid within the tubules, which is the cause of the pain response. Hydraulic conductance experiments showed that treatment of dentin with the 8% arginine-calcium carbonate toothpaste significantly reduced dentin permeability, *i.e.*, fluid flow, after just one treatment. Subsequent applications further reduced permeability, up to an 80% reduction from baseline after 14 treatments. The occluded dentin was resilient to typical pulpal pressures and to exposure to strong acid. The resistance of the dentin plug to an acid challenge was confirmed visually by CLSM. Occluded dentin specimens remained occluded in the CLSM experiment, even after two minutes of exposure to cola.

In summary, the arginine-calcium carbonate technology described in this Special Issue represents a significant breakthrough in the treatment and management of dentin hypersensitivity.[10,17,18] Two products have been clinically tested and shown to be effective in providing dentin hypersensitivity relief.[17-20] A toothpaste containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate has been clinically proven to be superior in relieving dentin hypersensitivity than a market-leading toothpaste containing 2% potassium ion.[17,18] In addition, a desensitizing prophylaxis paste containing 8% arginine, calcium carbonate, and prophylaxis-grade silica has been clinically proven to provide instant and lasting relief following a single professional application.[19,20] Importantly, these products do not possess the disadvantages of some occluding products, such as fluoride incompatibility, poor taste, or staining of the dentition or tongue. The arginine-calcium carbonate technology blocks the pathway to pain by occluding and sealing open dentin tubules. The acid resistance of the occluded layer ensures that the relief from sensitivity is lasting. In contrast to other products which occlude dentin tubules, this breakthrough technology is unique in that two of its key components, arginine and calcium, are found naturally in saliva, and the arginine and calcium carbonate work together to accelerate the natural mechanisms of occlusion, to deposit a dentin-like mineral containing calcium and phosphate within the dentin tubules and in a protective layer on the dentin surface.

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