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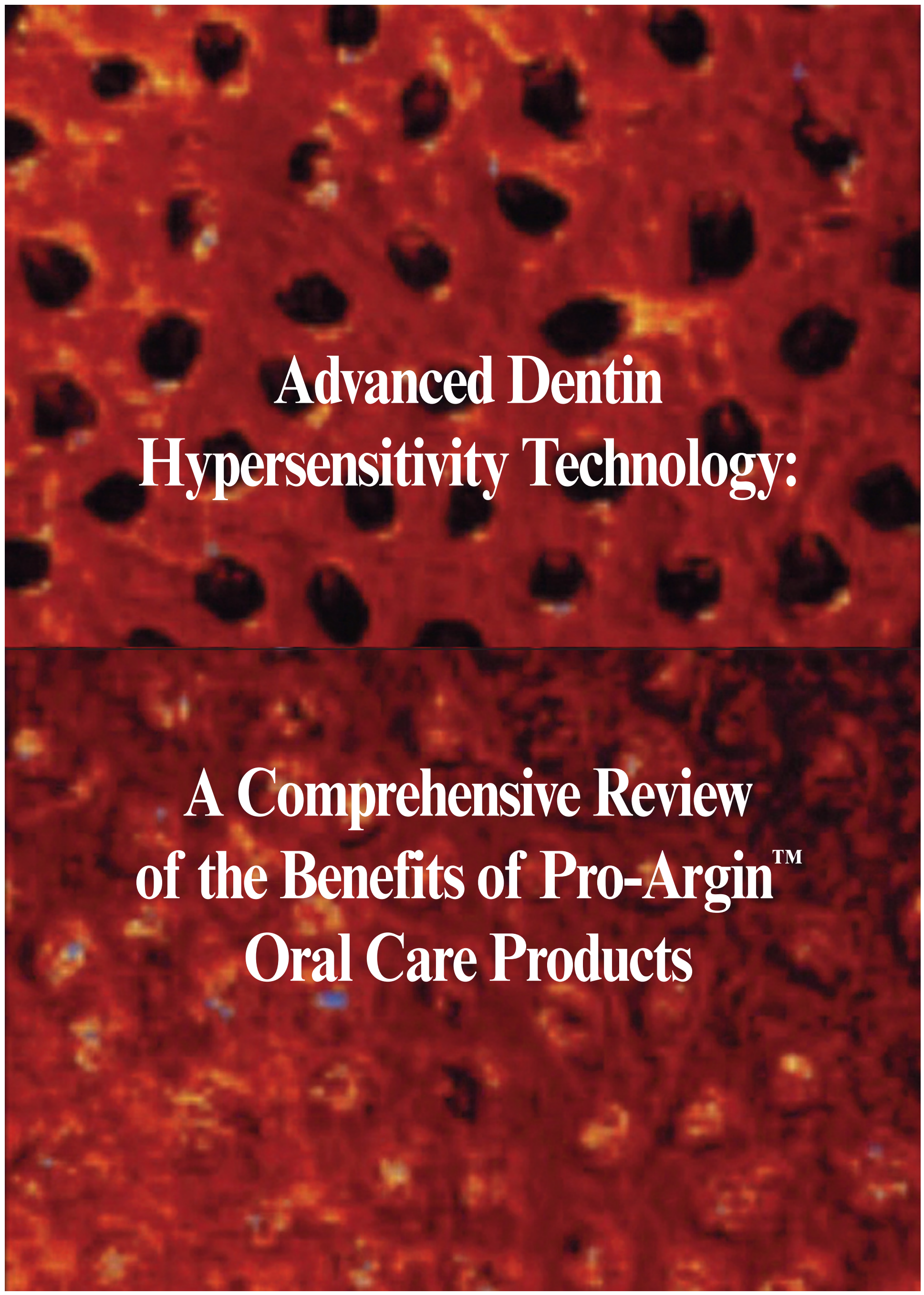

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Cover Image: Confocal Laser Scanning Microscopy images of dentin specimens before (top) treatment with an 8% arginine-calcium carbonate dentifrice with 1450 ppm fluoride as sodium monofluorophosphate. After five treatments (bottom), the dentin specimens were completely occluded.

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Advanced Dentin Hypersensitivity Technology: A Comprehensive Review of the Benefits of Pro-Argin™ Oral Care Products

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Abstract

Introduction: Arginine is an amino acid that is found naturally in saliva. When formulated correctly into oral care products, arginine is capable of plugging and sealing open dentin tubules, thereby providing relief from dentin hypersensitivity (Pro-Argin™ technology). The Colgate-Palmolive Company has used advanced science and technology to achieve immediate, as well as lasting relief from dentin hypersensitivity through the development of arginine-based in-office pastes, dentifrices, and oral rinses, all based on this Pro-Argin technology. This Supplement to *The Journal of Clinical Dentistry* reviews the published literature, which reports the laboratory and clinical studies that have been conducted on arginine-based oral care products.

Conclusion: The laboratory and clinical studies reviewed within this Supplement clearly indicate that the use of products based on this Pro-Argin technology provides superior relief from dentin hypersensitivity in comparison to products without a desensitizing agent. In addition, these products have been proven superior to products with other desensitizing agents. Taken together, these studies provide the basis and the necessary scientific support for dental professionals to recommend products with Pro-Argin technology to their patients who need relief from dentin hypersensitivity.

(J Clin Dent 2016;27(Suppl):S1-15)

Introduction

Dentin hypersensitivity occurs in patients with exposed dentin. It has been described as a short pain, occurring when the dentin encounters an external stimulus, such as thermal, evaporative, tactile, osmotic, or chemical, and cannot be credited to any form of dental defect or pathology.[1,2] The hydrodynamic theory proposes that the pain sensation is due to changes in the flow and/or volume of fluid within dentinal tubules, and is caused by the activation of mechanoreceptors in intratubular nerves or in the superficial pulp.[2] Therefore, once the external stimulus is no longer present, the pain goes away as the pressure within the dentinal tubule returns to normal.[3] There are several factors that have been identified as associated with dentin hypersensitivity. These include gingival recession, periodontal disease, deep tooth cracks, and the loss of enamel, cementum, and dentin which may be due to chemical erosion, mechanical abrasion, or even a tooth fracture.[2]

The existing literature reports a prevalence for dentin hypersensitivity ranging from 4–57%.[1] This percentage increases in periodontal patients, reaching 72–98%.[1] Most affected patients are in the 20–50-year-old range, with a peak reported to be in the age range of 30–40 years.[1,2] It has been shown that the most commonly affected teeth were premolars and molars.[4]

A comprehensive approach to dentin hypersensitivity management includes: 1) a correct diagnosis, which is compatible with the clinical description of dentin hypersensitivity and is based upon patient history and a dental examination; 2) differential diagnosis, to ensure that other conditions that might give rise to similar pain are excluded; 3) proper treatment of any secondary conditions that could induce symptoms similar to dentin hypersensitivity; 4) identification, as well as removal or minimization of etiologic and predisposing factors, particularly dietary and oral hygiene habits, especially those that are pertinent to abrasion and dental erosion; and 5) recommendation of treatment that is based upon the individual patient needs.[5]

There have been an assortment of chemicals, products, and measures that have been used by dental professionals in the office or by patients at home to fight dentin hypersensitivity.[2] For the most part, there are two approaches or mechanisms that can reduce or eliminate dentin hypersensitivity. First, the excited nerves in dentin tubules and pulp can be depolarized, which in turn disrupts the neural response to pain stimuli. Second, the exposed dentin can be sealed, which eliminates or minimizes the flow of dentin tubular fluid; this approach is based on the hydrodynamic theory.[2]

Historically, various agents, materials, and measures have been used to occlude dentin tubules. These have included strontium compounds, fluoride, casein phosphopeptide (CPP), potassium oxalate, resin sealers, as well as lasers.[2] So far, there has been little research on using lasers for reducing dentin hypersensitivity. Furthermore, the use of resin sealers and potassium oxalate is limited to certain patients for practical reasons, *e.g.*, not readily available, high costs, and lack of efficacy. Finally there has been minimal evidence supporting the use of fluoride (< 1500 ppm) in a dentifrice as a desensitizing agent.[2]

Dentifrices with 2% potassium salts as active ingredients have generally been recognized for their efficacy in reducing dentin hypersensitivity. However clinical data indicate that the effect from potassium salts is gradual. They require brushing twice daily for at least two weeks or longer to provide any significant relief from dentin hypersensitivity.[2] Furthermore, a Cochrane systematic review and meta-analysis of a subset of six randomized controlled clinical studies concluded that there was no clear evidence to support the clinical efficacy of dentifrices containing potassium salts in reducing dentin hypersensitivity.[6]

More recently, a technology using arginine has been introduced to control dentin hypersensitivity.[2] Arginine, an amino acid found in saliva, is not capable of quickly plugging and sealing open dentin tubules and thereby providing immediate reduction of dentin hypersensitivity. However, an arginine-based desensitizing prophylaxis paste, originally called ProClude® Desensitizing Prophylaxis Paste (Ortek Therapeutics, Inc., Roslyn Heights, NY, USA), demonstrated that it could provide instant sensitivity relief when applied to sensitive teeth following scaling and root planning. Additionally, this single application was able to provide sensitivity relief that lasted for at least 28 days.[2] This arginine-based technology was purchased in 2008 by the Colgate-Palmolive Company, who further developed a series of arginine-based in-office pastes, dentifrices, and oral rinses, all based on this Pro-Argin™ technology and marketed under the Colgate® Sensitive Pro-Relief™ and elmex® Sensitive Professional™ brands.

The laboratory and clinical studies reviewed within this Supplement clearly indicate that the arginine-based in-office pastes, dentifrices, and oral rinses provide superior dentin hypersensitivity efficacy, as well as provide other desired consumer benefits.

Formula

Arginine

Arginine is one of the twenty amino acids and is classified as a semi-essential amino acid that can be produced in the human body or obtained via dietary proteins. It is found in a variety of both animal and plant sources, and is sold as a dietary supplement. The normal daily intake of arginine from dietary sources in an American diet ranges from about 3–6 grams.[7] In most healthy adults, endogenous synthesis of arginine is sufficient, so the ingestion of food and digestion of dietary proteins to obtain arginine is not essential. Infants, small children, and compromised adults, however, are unable to produce arginine in the body, so dietary supplementation is essential. This is why arginine is classified as a semi-essential amino acid.[8]

In the oral cavity, arginine is secreted in free form via salivary glands at concentrations averaging about 50 µM. It is abundant in salivary proteins.[9] The histidine-rich salivary proteins, as an example, contain approximately 10–20 mol-percent arginine, which can be readily released by salivary or bacterial proteases.[10] Various proteases can also release free arginine from foods that are ingested.[11] In addition, free arginine is also found in mature dental plaque at concentrations of approximately 200 µM.[12]

Arginine (Figure 1) is one of three basic amino acids that are positively charged and polar at physiological pH. The side chain of arginine is a guanidinium group that is positively charged across the pH spectrum, which enables arginine to bind to negatively charged surfaces.

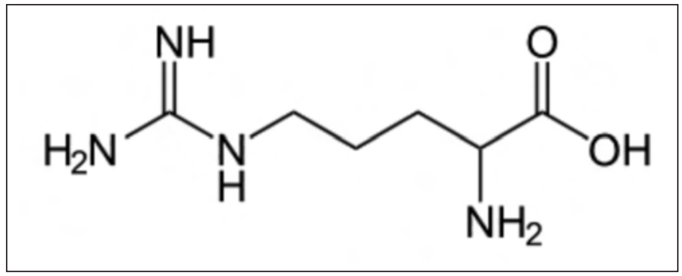

Figure 1. *Arginine.*

In-Office Paste and Dentifrice

The Pro-Argin technology in the in-office paste and dentifrice consists of 8% arginine and calcium carbonate. The in-office paste is designed to be used by dental professionals on their patients with dentin hypersensitivity. This in-office paste can be used either before or after dental procedures, such as prophylaxis or scaling. A one-time application can provide up to four weeks of sensitivity relief. The dentifrice is designed for twice-daily use at home. Instant relief is achieved when the dentifrice is applied directly, *e.g.*, with a finger-tip, to a sensitive tooth and massaged for one minute. Lasting relief occurs when the sensitive areas of each tooth are brushed twice daily.

Through electrostatic physical attraction, arginine can bind to the negatively charged dentin surfaces or to the open dentin tubules. Calcium carbonate is poorly soluble and has a positive surface charge. Because of its polarity, arginine binds to dentin. Within the open dentin tubules, it can attract calcium carbonate to it to form occlusive plugs that seal the open dentin tubules. Due to its alkalinity, this occlusive complex can react with the calcium and phosphate ions in dentin fluid, as well as in saliva to make the occlusive plug contiguous with the dentin tubule walls and even more secure within the confines of the dentin tubule.[13] Laboratory studies described elsewhere in this supplement support that this mechanism of action of the Pro-Argin technology forms a protective layer on the dentin surface, as well as a dentin-like material plug within the open dentin tubule that is resistant to acid challenge.

Oral Rinse

As a result of the efficacy of the 8% arginine-calcium carbonate-based desensitizing products, a mouthrinse, consisting of 0.8% arginine, was developed to complement the dentifrice.[14] The mouthrinse technology relies on the combination of L-arginine, polyvinylmethyl ether/maleic acid copolymer (PVM/MA), and pyrophosphates. The mode of action is based on the decrease in dentin permeability, which is accomplished by dentin occlusion. Arginine has an affinity for dentin, and acts to promote the adhesion of materials to the dentin surface. This specific combination of arginine, PVM/MA copolymer, and pyrophosphates, in the appropriate pH and ionic-strength environment, has been proposed to form an adhesive complex that builds up with continued use and results in the reduction of hydraulic conductance, which is ultimately linked to the mitigation of dentin hypersensitivity.[14]

Dentin Hypersensitivity

Laboratory Studies

The mechanism of action of the arginine technology *in vitro* has been elucidated using several state-of-the art methods.[15-20] These techniques have demonstrated that this arginine technology can provide rapid and complete occlusion of the open, exposed dentin tubules. Furthermore, this occlusion is resistant to acid challenge.

The techniques that have been used include confocal laser scanning microscopy (CLSM), scanning electron microscopy (SEM), energy dispersive x-ray (EDX), atomic force microscopy (AFM), electron spectroscopy for chemical analysis (ESCA) including Secondary Ion Mass Spectroscopy (SIMS), hydraulic conductance, and near infrared spectroscopy (NIR).

Confocal Laser Scanning Microscopy. Petrou, *et al.*[15] used CLSM to compare dentin specimens treated with four test products: a calcium carbonate-containing dentifrice (pH = 9); an 8% arginine-calcium carbonate dentifrice with 1450 ppm fluoride as sodium monofluorophosphate (SMFP; pH = 9); an 8% arginine-dical dentifrice with 1450 ppm fluoride as SMFP (pH = 7); and an 8% arginine-calcium carbonate desensitizing paste with high-cleaning silica (pH = 9). The results, as shown in Figure 2, indicate that within five applications dentin specimens treated with either the 8% arginine-calcium carbonate dentifrice or the 8% arginine-calcium carbonate desensitizing paste were completely occluded. Occlusion did not occur in the absence of arginine or at a neutral pH. In addition, the presence of fluoride did not impact occlusion.

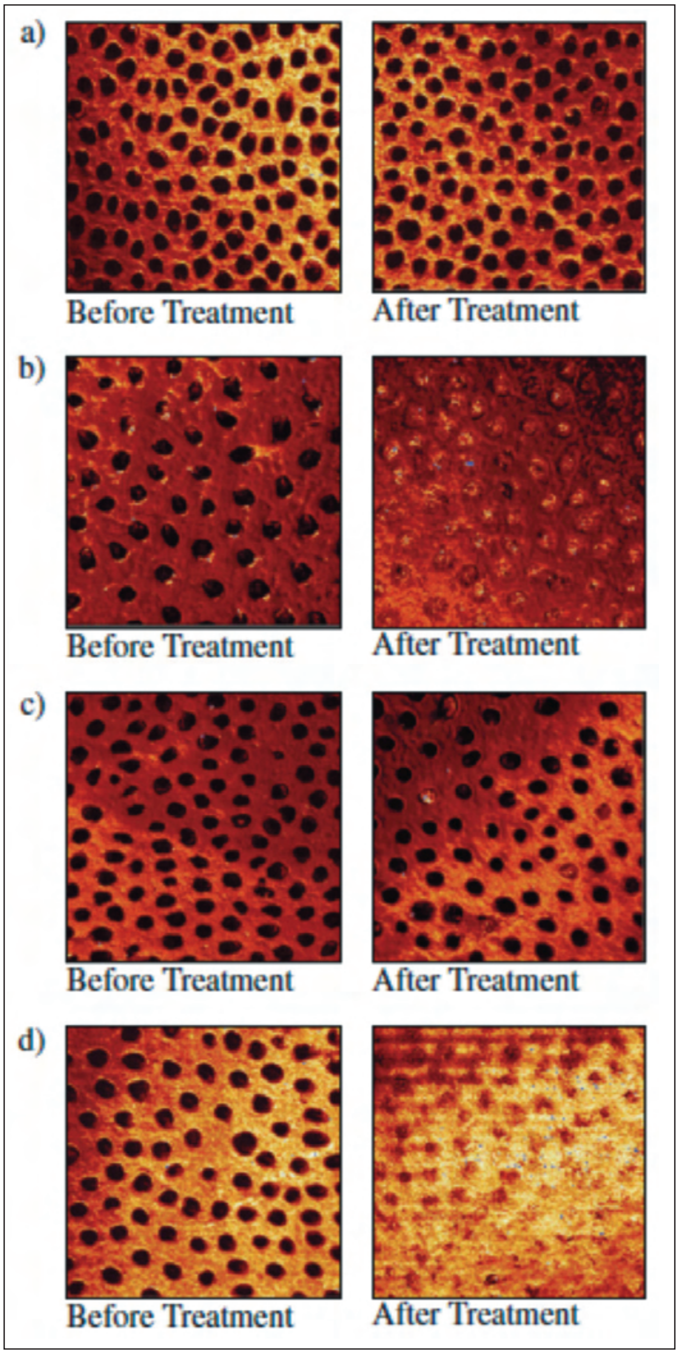

Figure 2. *Dentin specimens before and after treatment with a) $CaCO_3$ dentifrice without fluoride or arginine; b) $CaCO_3$ dentifrice with 8% arginine and 1450 ppm MFP; c) dical dentifrice with 8% arginine and 1450 ppm MFP; and d) desensitizing prophlyaxis paste with 8% arginine and calcium carbonate (Reprinted from Petrou, et al., J Clin Dent 2009[15]).*

Previously occluded dentin samples were exposed to cola for two minutes to simulate consumption of an acidic beverage. CLSM measurements indicate that the occluded dentin samples remain occluded after exposure to cola (Figure 3). These results demonstrate that the occluding layer is resistant to an acid challenge from a typical beverage that may be consumed following use of the product.[15]

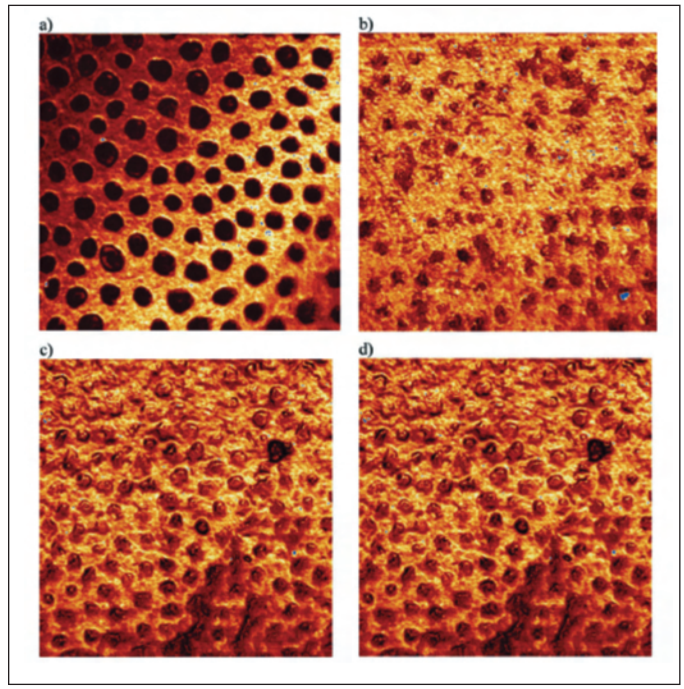

Figure 3. *Confocal images of a) untreated dentin; b) dentin treated with the prophylaxis paste with 8% arginine and calcium carbonate; c) treated dentin after one-minute exposure to cola; and d) treated dentin after two minutes total exposure to cola. (Reprinted from Petrou, et al., J Clin Dent 2009[15]).*

Lavender, *et al.*[16] evaluated a dentifrice with 8% arginine, high-cleaning calcium carbonate, and 1450 ppm fluoride as SMFP using CLSM. The results, as shown in Figure 4, indicate after treatment there is complete occlusion of the dentin tubules. They also evaluated the acid resistance following the method of Petrou, *et al.*[15] The results confirm that the tubules remained occluded and are resistant to an acid challenge.

Mello, *et al.*[17] used both the reflectance mode and the fluorescent mode of CLSM to demonstrate the penetration of the 0.8% arginine mouthrinse into open tubules. Figure 5 shows the fluorescence images taken after treatment with the 0.8% arginine mouthrinse. The bright points indicate the presence of the arginine mouthrinse throughout the surface, while the side view indicates penetration of the arginine mouthrinse inside the tubule walls. In contrast to the arginine mouthrinse, very little evidence on the dentin surface (xy image) or in the tubules (xz image) could be visualized for the

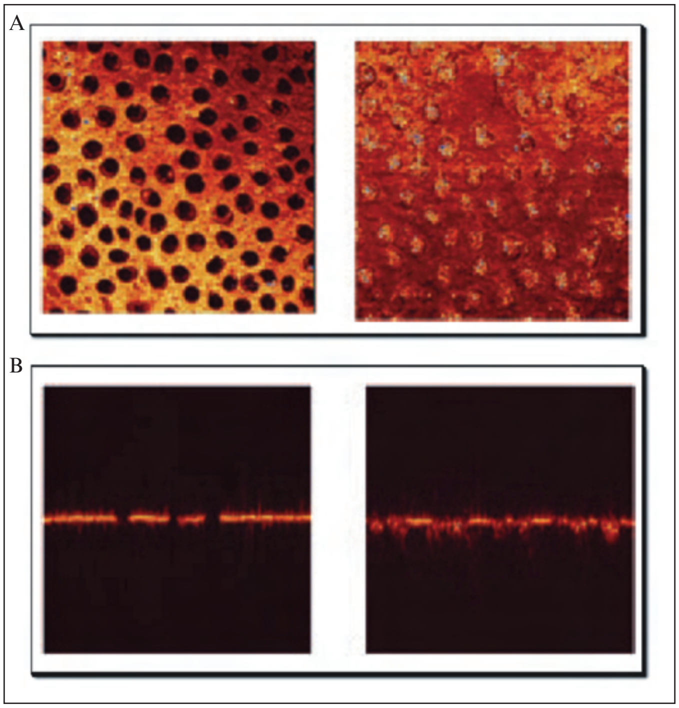

Figure 4. *Dentin specimens before (on left) and after (on right) treatment with the Pro-Argin formula. A. XY view. B. XZ view. (Reprinted from Lavender, et al., Am J Dent 2010[16] with permission).*

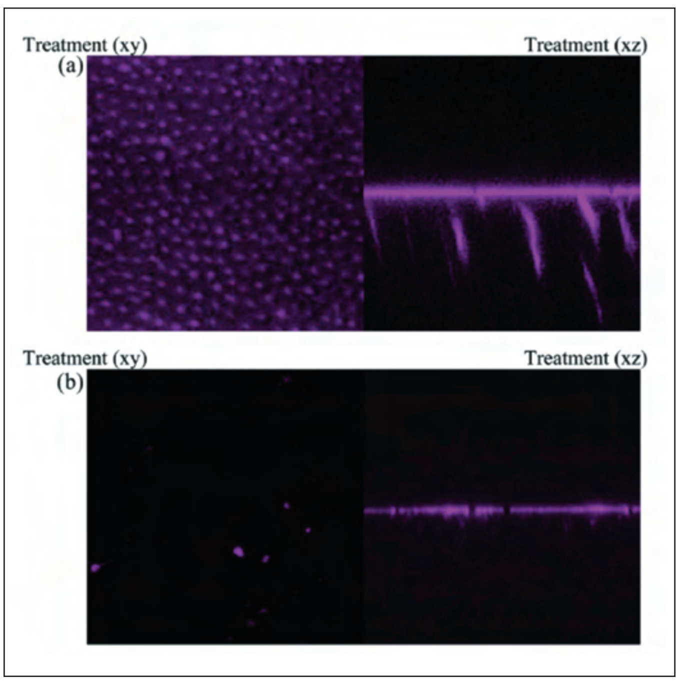

Figure 5. *(a) CLSM images (fluorescence mode) of dentin surface treated with arginine mouthwash. Image scale 100 µm x 100 µm. (b) CLSM images (fluorescence mode) of dentin surface treated with the negative control mouthwash. Image scale 100 µm x 100 µm. (Reprinted from Mello, et al., J Dent 2013[17] with permission)*

negative control mouthrinse. These images prove that the arginine mouthrinse penetrates inside the tubules and deposits on the dentin surface.

Scanning Electron Microscopy. High resolution images of dentin surfaces treated with the 8% arginine-calcium carbonate desensitizing paste have been obtained using SEM.[15] Analysis of these images confirms the CLSM findings, and indicates that the 8% arginine-calcium carbonate desensitizing paste effectively occludes dentin tubules as shown in Figure 6. Figure 7 shows SEMs of the dentin surfaces after freeze-fracturing, which allows determination of occlusion as a function of depth.

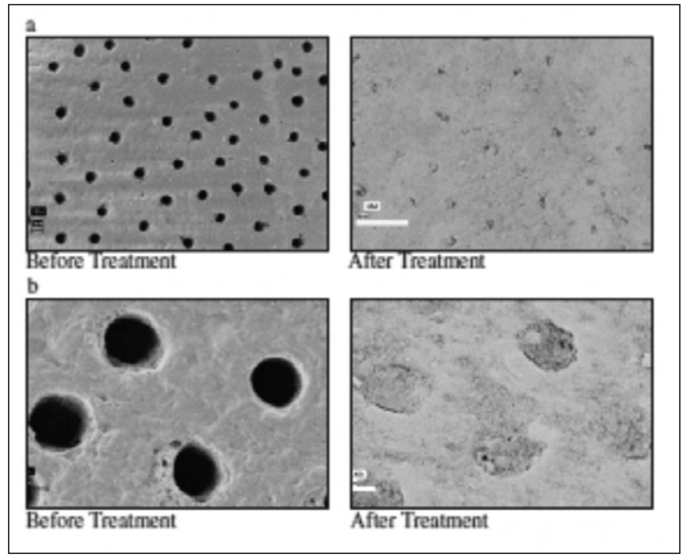

Figure 6. *Scanning electron micrographs of dentin surfaces before and after treatment with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate. a) 2000X magnification and b) 10,000X magnification. (Reprinted from Petrou, et al., J Clin Dent 2009[15])*

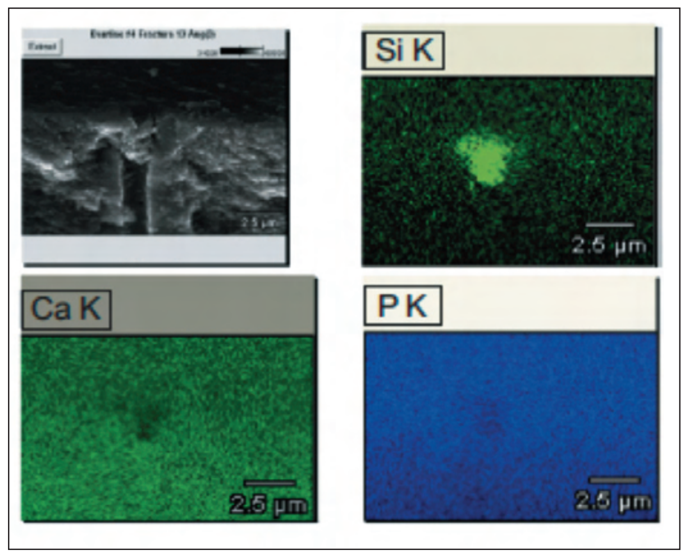

Figure 7. *Scanning electron micrographs of freeze-fractured dentin surfaces after treatment with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate. Left figure illustrates SEM freeze-fracture and right illustrates EDX chemical mapping. (Reprinted from Petrou, et al., J Clin Dent 2009[15])*

Lavender, *et al*.[16] used SEM to confirm the CLSM findings, and indicated that the dentifrice with 8% arginine, high-cleaning calcium carbonate, and 1450 ppm fluoride as SMFP effectively occludes dentin tubules. Additional work by Li, *et al.* investigated the laboratory changes in dentin tubule occlusion morphology during short-term use of the 8% arginine-calcium carbonate dentifrice.[18] The test treatment was applied to a dentin disk twice daily for 10 days using a brushing cycle of 200 strokes. The disks were then soaked in filtrated human saliva. The two other products were a 10% strontium chloride dentifrice (Sensodyne Original) and a professional remineralizing treatment paste (GC Tooth Mousse). All products created a smear layer on the dentin surface that significantly reduced the diameter of dentin tubules after treatment. Compared to the dentin tubule area (72.02 ± 7.23 μm^2) on the disks treated with the negative control, disks treated with the 8% arginine-calcium carbonate dentifrice, Sensodyne Original, and GC Mousse had dentin tubule areas of 2.10 ± 0.42 μm^2, 10.11 ± 2.83 μm^2, and 30.40 ± 4.04 μm^2, respectively. The differences among the three treatments were statistically significant, with the 8% arginine-calcium carbonate dentifrice having the lowest average tubule area as compared to the other two treatments, suggesting that it provides a significantly higher level of tubule occluding effect than the other products.[18]

Energy Dispersive X-Ray. Petrou, *et al.* further examined these freeze-fractured dentin surfaces using EDX, which allowed for a chemical characterization.[15] They found that the surface layer on the dentin primarily consisted of calcium and phosphate. In addition, silica was found with the calcium and phosphate

Atomic Force Microscopy. Petrou, *et al.*[15] used AFM to evaluate dentin specimens before and after treatment with the 8% arginine-calcium carbonate desensitizing paste. As shown in Figure 8, the arginine-calcium carbonate technology is extremely effective in occluding open dentin tubules. AFM was further utilized by Mello, *et al.*[17] to demonstrate the deposition of the arginine mouthrinse onto the dentin surface. Figure 9 shows a dentin tubule before and after treatment with the mouthrinse, indicating occlusion.

Electron Spectroscopy for Chemical Analysis. ESCA images of a dentin surface prior to treatment will show high levels of carbon, oxygen, and nitrogen. In comparison, there is significantly less calcium and phosphorus.[15] This is consistent with a demineralized dentin surface and an exposed collagen matrix. There was no carbon as carbonate measured on the surface. The amount of carbon and nitrogen significantly decreased, while carbon associated with carbonate was detected on the surface after treatment with the 8% arginine-calcium carbonate desensitizing paste. Furthermore, levels of calcium, oxygen, and phosphorus significantly increased and are consistent with a remineralization of the dentin surface, as well as dentin tubule occlusion by a dentin-like mineral containing calcium and phosphate, along with calcium carbonate.

Lavender, *et al.*[16] used ESCA to analyze the dentin surface before and after treatment with the dentifrice containing 8% arginine, a high-cleaning calcium carbonate, and 1450 ppm fluoride as SMFP. Before treatment, there were elevated levels of carbon, oxygen, and nitrogen on the surface, with significantly lower amounts of calcium and phosphorus. These results are consistent with a demineralized dentin surface allowing the tubules to open and the collagen matrix to be exposed. No carbon, as carbonate, was detected. Treatment with the arginine-containing dentifrice resulted in a dramatically different surface composition. As shown by Petrou, *et al.*,[15] levels of carbon and nitrogen decreased, while carbon, as carbonate, was detected. Levels of calcium, oxygen, and phosphorus increased, which indicates a remineralization of the dentin surface along with occlusion of the dentin tubules by a dentin-like mineral containing calcium and phosphate together with calcium carbonate.

ESCA and SIMS were used to assess the chemical composition before and after treatment with the arginine mouthrinse on dentin discs.[17] Prior to treatment, the composition of the dentin discs was consistent with that of demineralized untreated dentin. After treatment with the arginine mouthrinse, increased amounts of sodium were measured, as well as an increase in the potassium to calcium ratio. In addition, potassium was now present. These results are consistent with the deposition of the arginine mouthrinse, which contains tetrapotassium pyrophosphate and tetrasodium pyrophosphate. Deposition of arginine is supported by increased levels of N+ (ESCA) and a mass peak at 175 amu (SIMS). Finally, increases in peak intensity ratios involving PVM/MA fragment ions at 45 amu and 59 amu support its deposition.

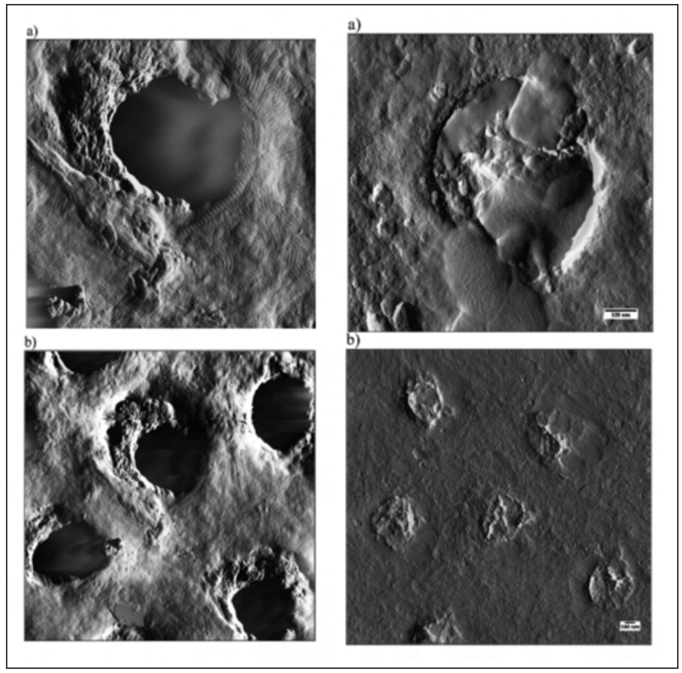

Figure 8. *On left, Atomic Force Microscope images of untreated dentin. a) a single tubule and b)multiple tubules. On right, Atomic force microscope images of dentin treated with the desensitizing prophylaxis paste containing 8% arginine and calcium carbonate. a) a single tubule and b) multiple tubules. (Reprinted from Petrou, et al., J Clin Dent 2009[15])*

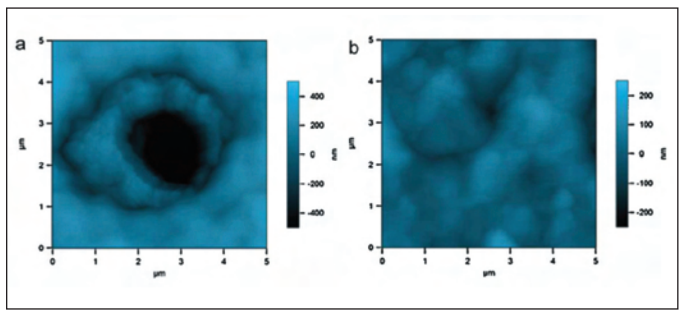

Figure 9. *AFM topography images of a dentinal tubule before and after treatment with the arginine mouthwash. (Reprinted from Mello, et al., J Dent 2013[17] with permission)*

Hydraulic Conductance. Hydraulic conductance measurements determine the amount of fluid flow within dentin tubules. Petrou, *et al.*[15] determined that one application of the 8% arginine-calcium carbonate dentifrice reduced dentin permeability by more than 63%, and by more than 80% after 14 treatments as compared to the pretreatment values.

Hydraulic conductance was also used by Patel, *et al.*[19] to examine the dentin permeability of the 8% arginine-calcium carbonate dentifrice with 1450 ppm fluoride as SMFP, as compared to another dentifrice with 8% strontium acetate and 1040 ppm fluoride as sodium fluoride. Following the method of Pashley, *et al*.,[21] hydraulic conductance measurements were made before any treatment by the test products, as well as after treatments. In addition, measurements were made before and after an acid challenge. The treatments and acid challenge were performed sequentially, with the first treatment being a fingertip application of the product, followed by two brushing treatments. The acid treatments tested included grapefruit juice, orange juice, and 6% citric acid. The results are shown in Figure 10, with statistically significantly greater reductions in fluid flow for the 8% arginine-calcium carbonate dentifrice as compared to the 8% strontium acetate dentifrice after each treatment, as well as after each of the acid challenges.

Mello, *et al*.[20] used hydraulic conductance to measure the dentin permeability efficacy of a 0.8% arginine, PVM/MA copolymer, pyrophosphates, and sodium fluoride-containing mouthrinse. Figure 11 shows that there was a statistically significant difference between the arginine-containing mouthrinse (42%) and the negative control mouthrinse (9%). Furthermore, there was no significant difference in dentin permeability before and after an acid challenge.

Near Infrared Spectroscopy. Mello, *et al.*[17] used near infrared spectroscopy to detect the presence of arginine, which has a unique fingerprint at 1530 nm, on the dentin surface. Figure 12 shows that arginine was detected within the first three treatments with the 0.8% arginine mouthrinse, with the concentration of the arginine increasing with the number of treatments.

Overall Conclusion from the Laboratory Studies with an 8% Arginine-Calcium Carbonate In-office Desensitizing Paste, an 8% Arginine-Calcium Carbonate Dentifrice, or a 0.8% Arginine/PVM/MA Copolymer/Pyrophosphate Mouthrinse

The overall conclusion from the laboratory studies discussed in this section is that use of these products provides occlusion of open dentin tubules, which is resistant to acid challenge.

Clinical Studies

All the clinical studies reported in this Supplement were conducted in accordance with Good Clinical Practice. In addition, all study subjects signed the appropriate informed consent. The clinical protocol and related documents for each study were reviewed and approved by a local ethics committee (Institutional Review Board).

Sensitivity Measurements

Tactile (Yeaple Probe). In most studies, tactile sensitivity was evaluated with a Model 200A Electronic Force-Sensing Probe, also known as a Yeaple Probe (XiniX Research, Inc, Portsmouth, NH, USA). Scores were recorded in grams of applied force, ranging from 10 to 100 g. Any subject entering into the clinical study was required to have at least two hypersensitive teeth, which were anterior to the molars. In addition, the tactile stimulus scores for these two teeth had to be within the range of 10–50 g as measured by the Yeaple Probe. With the force set to 10 g, the Yeaple Probe tip passes over the exposed dentin on the buccal surface of the selected teeth, apical to the cemento-enamel junction. Additional passes are made with the applied force increased in 10 g increments. This continues until the subject indicates discomfort or until a force of 50 g is reached, which is the upper limit for inclusion in the study. Higher scores indicate lower levels of dentin hypersensitivity.[22-24]

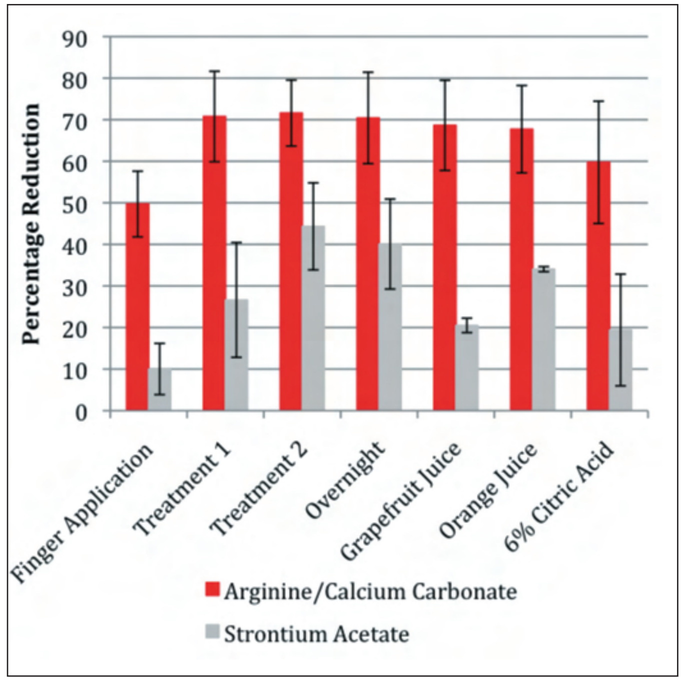

Figure 10. *Hydraulic conductance results after treatment and after exposure to acid challenge. (Reprinted from Patel, et al., J Clin Dent 2011[19])*

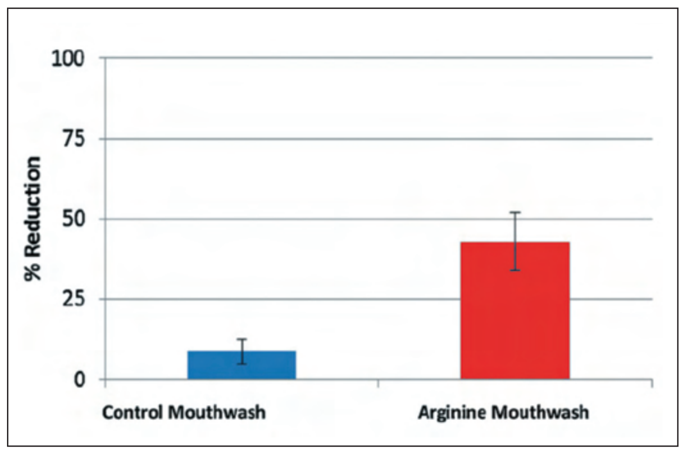

Figure 11. *Dentin fluid reduction of arginine mouthwash as compared to negative control mouthwash. (Reprinted from Mello, et al., J Dent 2013[20] with permission)*

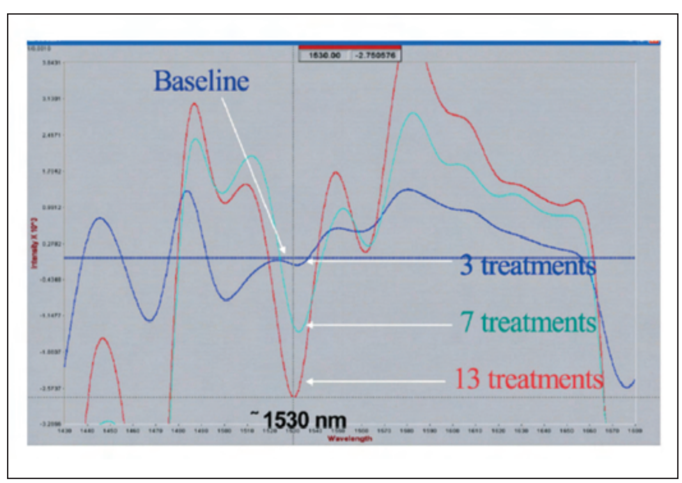

Figure 12. *NIR spectra of dentine surface treated with Arginine mouthwash. (Reprinted from Mello, et al., J Dent 2013[17] with permission)*

Air-Blast (Schiff). Sensitivity in the clinical studies was also evaluated by directing air onto the buccal root surface of each tooth. The air component of a dental air/water syringe was placed one centimeter away from each tooth. The adjacent proximal teeth were shielded from the air blast by placing two fingers to block the air flow. The air was applied at a fixed temperature (70°F ± 3°F) and a fixed pressure (60 psig ± 5 psig) for one second. The panelists responded to the air blast and their scores were recorded according to the air sensitivity scale.[23] Only those teeth with a score of 2 or 3 were selected for inclusion. With this scale, higher scores indicated higher levels of dentin hypersensitivity.

Sensitivity Score	Sensitivity Description
0	Subject (tooth) does not respond to air stimulus
1	Subject (tooth) responds to air stimulus, but does not request discontinuation of stimulus
2	Subject (tooth) responds to air stimulus, and requests discontinuation of stimulus or moves from stimulus
3	Subject (tooth) responds to air stimulus, considers stimulus as painful, and requests discontinuation of stimulus

Tactile (Jay Probe). The Jay Sensitivity Sensor Probe (Jay Probe Model 2612, Global Health Research Group, India) is a relatively recent device for use in the clinic to assess tactile dentin hypersensitivity.[25,26] The Jay Probe is calibrated at the factory and comes equipped with a microprocessor and a digital display. It is programmed to apply force in 10 g increments, with each increment representing a force range. The examiner controls the application of the force range through use of a foot pedal. The Jay Probe is applied in a manner similar to that of the Yeaple Probe, and a force of 50 g is considered the cut-off for inclusion in a study. Higher scores indicate lower sensitivity. Research by Sowinski, *et al*. demonstrates the utility of the Jay Probe in the clinical setting. Furthermore, their research indicates a significant correlation between the Jay Probe and the other methods used to measure dentin hypersensitivity.[27]

Visual Analog Scale. The Visual Analog Scale (VAS) is used in dentin hypersensitivity studies to have the subjects self-assess the amount of pain that they experience, in the absence of any stimuli.[28-30] Subjects are presented with a 10 cm line, either on a sheet of paper or on a computer touch screen. The two extremes represent the limits (0 cm = no pain; 10 cm = highest pain). VAS data are recorded as the distance between the zero point and the mark made by the subject.

In-Office Desensitizing Paste

Immediate Effect. Table I presents the immediate dentin hypersensitivity effects of an 8% arginine-calcium carbonate desensitizing paste from six independent and double-blind clinical studies, as compared to an ordinary pumice-based prophylaxis paste. These studies demonstrate the superior efficacy of the 8% arginine-calcium carbonate desensitizing paste when applied after a scaling procedure, as well as before or concurrent with a dental prophylaxis.[1,31-35] Statistically significant improvements in dentin hypersensitivity were observed immediately after product application using both the Yeaple Probe and air-blast measurements.

Lasting Effect. Table I also presents the long-lasting dentin hypersensitivity effects of an 8% arginine-calcium carbonate desensitizing paste from two independent and double-blind clinical studies, as compared to an ordinary pumice-based prophylaxis paste. These studies demonstrate the superior efficacy of the 8% arginine-calcium carbonate desensitizing paste when applied after a scaling procedure.[31,34] Statistically significant improvements in dentin hypersensitivity were observed up to four weeks after product application using both the Yeaple Probe and air-blast measurements.[31]

Against Other Technologies. Finally, Table I presents the results of one study by Li, *et al.* in which the dentin hypersensitivity efficacy of the 8% arginine-calcium carbonate desensitizing paste was evaluated against a competitive prophylaxis paste (MI Paste Plus with CPP-

Table I
Dentin Hypersensitivity Efficacy of 8% Arginine-Calcium Carbonate Desensitizing Paste Against a Control In-Office Paste

Reference	Investigators	Location	N	Immediate*		4 Weeks*		12 Weeks*	
				Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast
31	Schiff, et al. 2009	California After scaling	68[1]	79%	34.1%	149.6%	40.6%	-1.85%**	-1.1%**
32	Hamlin, et al. 2009	Pennsylvania[1] Before Prophy	45[1]	110.0%	41.9%				
1	Hamlin, et al. 2012	Pennsylvania After Scaling	95[1]	49.8%	26.0%				
33	Tsai, et al. 2012	New Jersey Before Prophy	66[1]		79.6%				
34	Li, et al. 2013	California After Scaling	80[1] 80[2]	59.4% 56.7%	40.9% 40.9%	64.2% 59.0%	51.8% 54.3%		
35	Collins, et al. 2013	Dominican Republic concurrent with Prophy	50[1]		24.4%				

* Percentage change calculated as the mean of the 8% arginine-calcium carbonate desensitizing paste relative to the mean of the control in-office paste at each time point. A positive value indicates an improvement for the 8% arginine-calcium carbonate desensitizing paste relative to the control in-office paste.
**Indicates no significant difference ($p > 0.05$) between the 8% arginine-calcium carbonate desensitizing paste and the control paste.
[1] Nupro Prophylaxis Paste (Pumice)
[2] MI Paste Plus (CPP-ACP)

ACP).[34] In this study, in which the efficacy was determined immediately after a dental scaling procedure, the 8% arginine-calcium carbonate desensitizing paste provided immediate and long-lasting efficacy as measured by both the Yeaple Probe and the air blast technique.

Overall Conclusion from Six Clinical Efficacy Studies on Dentin Hypersensitivity with an 8% Arginine-Calcium Carbonate Desensitizing Paste

The overall conclusion from the six independent, randomized clinical studies shown in Table I is that a desensitizing paste containing 8% arginine and calcium carbonate provides significant and clinically meaningful immediate and long-lasting relief of dentin hypersensitivity, as compared to the similar use of a control in-office paste.

Dentifrice

Immediate. Direct topical application of a dentifrice is a novel way to deliver an immediate dentin hypersensitivity benefit. In this method, after baseline dentin hypersensitivity measurements, qualifying subjects self-apply a "pea-sized" amount of dentifrice directly onto the buccal-cervical area of exposed dentin of the affected tooth, and gently massage the tooth for 60 seconds. Immediately after application, follow-up measurements of dentin hypersensitivity are made. Subjects are then provided with their dentifrice for use at-home and instructed to brush their teeth twice daily, for one minute each time, until they return either three or seven days later for follow-up measurements.

Table II presents the immediate dentin hypersensitivity results from four independent and double-blind clinical studies, which compared the 8% arginine, calcium carbonate, sodium monofluorophosphate dentifrice to a negative control dentifrice.[36-39] All five of the test products, including one that contained high-cleaning calcium carbonate instead of calcium carbonate, provided statistically significant improvements in dentin hypersensitivity, both immediately after product application, where the efficacy ranged from 82.0% to 180.2% improvement as measured by the Yeaple Probe, with a mean improvement of 115.1%, and from 41.3% to 58.0% improvement in air blast scores, with a mean improvement of 47.1%. After three to seven days of at-home brushing, this improvement was sustained, with a range of improvement of 43.9% to 181.2% and a mean improvement of 135.4% for the Yeaple Probe, and a range of 53.2% to 70% and a mean of 59.9% for air blast improvement.

In addition to these studies, Schiff, *et al*. compared the proven direct topical application of the dentifrice to a method in which the dentifrice was applied to a cotton swab applicator, and then massaged onto the identified hypersensitive teeth for one minute.[40] Measurements taken immediately after product application showed that both application methods demonstrated a statistically significant improvement in dentin hypersensitivity. Furthermore, this improvement was maintained after seven days of at-home tooth brushing. Statistical analysis indicated that the two methods were equivalent in their control of dentin hypersensitivity at both time points.

Lasting Relief. Table III presents the dentin hypersensitivity results from five independent and double-blind clinical studies, which compared the 8% arginine, calcium carbonate, sodium monofluorophosphate dentifrice to a negative control dentifrice.[41-45] During these studies, the subjects brushed at home for one minute, twice daily, for up to eight weeks. All six of the test products, including one that contained high-cleaning calcium carbonate instead of calcium carbonate, provided statistically significant improvements in dentin hypersensitivity after two, four, and eight weeks of tooth brushing. After two weeks, there was a mean improvement in dentin hypersensitivity as measured by the Yeaple Probe of 67.5% (range: 61.0%–81.9%) and by air-blast of 39.5% (range: 30.5%–55.6%). Dentin hypersensitivity efficacy was further improved after four weeks of brushing as measured by the Yeaple Probe of 95.9% (range: 67.8%–140.1%) and by air blast of 60.4% (range: 51.7%–69.8%). Finally, after eight weeks of brushing, there was even more efficacy as measured by the Yeaple Probe of 107.2% (range: 59.4%–152.2%) and air blast of 78.6% (range: 74.4%–82.1%). In two of these studies,[44,45] Jay Probe and VAS measurements were also made. In those studies, reduction in dentin hypersensitivity ranged from 67.4% after two weeks of use to 155.5% at eight weeks, as measured by the Jay Probe. VAS results showed a similar trend with a 25.8% reduction after two weeks but increasing to 72.2% after eight weeks.

Against Other Technologies. Table IV presents the immediate dentin hypersensitivity results from three independent and double-blind clinical studies, which compared the 8% arginine, calcium carbonate, sodium monofluorophosphate dentifrice to a dentifrice containing an alternative technology, either potassium ion or strontium ion.[36,37,39] All three of the studies demonstrated that the arginine technology was superior to either the potassium or strontium technology in providing immediate dentin hypersensitivity relief,

Table II
Immediate Dentin Hypersensitivity Efficacy of 8% Arginine-Calcium Carbonate Dentifrice Against Negative Control Dentifrice

Reference	Investigators	Location	N	Immediate*		3 Day*		7 Day*	
				Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast
36	Ayad, *et al.* 2009	Canada	81	139.5%	49.6%	136.1%	53.2%		
37	Nathoo, *et al.* 2009	New Jersey	83	180.2%	58.0%	181.2%	70.9%		
38	Fu, *et al.* 2010	China	81**	82.0%	41.3%	115.7%	58.5%		
			81	82.7%	41.7%	108.8%	57.0%		
39	Li, *et al.* 2011	California	100	91.0%	44.8%			43.9%	54.1%
		Mean		115.1%	47.1%	135.4%	59.9%		
		Range		82.0% – 180.2%	41.3% - 58.0%	108.8% - 181.2%	53.2% - 70.9%		

* Percentage change calculated as the mean of the 8% arginine-calcium carbonate dentifrice relative to the mean of the negative control dentifrice at each time point. A positive value indicates an improvement for the 8% arginine-calcium carbonate dentifrice relative to the negative control dentifrice.
**Contains high-cleaning calcium carbonate.

and then maintaining it for up to seven days through the use of an at-home brushing regimen.

Overall Conclusion from Four Clinical Efficacy Studies on Immediate Dentin Hypersensitivity with an 8% Arginine-Calcium Carbonate Dentifrice

The overall conclusion from the four independent and randomized clinical studies shown in Tables II and IV is that a dentifrice containing 8% arginine and calcium carbonate provides significant and clinically meaningful relief of dentin hypersensitivity immediately after treatment as compared to the similar use of a positive and / or a negative control dentifrice.

Table V presents the dentin hypersensitivity results from six independent and double-blind clinical studies, which compared the 8% arginine, calcium carbonate, sodium monofluorophosphate dentifrice to a dentifrice containing an alternative technology, either potassium ion or strontium ion, in an at-home brushing program that lasted up to eight weeks.[42,46-50] Statistically significant improvements in dentin hypersensitivity were observed between the arginine dentifrice and the other dentifrices as early as after two weeks of brushing. No differences were observed after three days of brushing in one study, while in another study after one week Yeaple Probe measurements showed a difference in favor of the arginine dentifrice, while there was no difference observed by air blast measurements. Taken together, all six studies demonstrate that the arginine technology was superior to either the potassium or strontium technology in providing dentin hypersensitivity relief after two weeks of use, and this superiority is maintained after eight weeks of use.

Overall Conclusion from Fourteen Clinical Efficacy Studies on Dentin Hypersensitivity with an 8% Arginine-Calcium Carbonate Dentifrice

The overall conclusion from the fourteen independent clinical efficacy studies shown in Tables II through V is that a dentifrice containing 8% arginine and calcium carbonate provides a significant and clinically meaningful reduction of dentin hypersensitivity as compared to the similar use of a positive and / or a negative control dentifrice.

Mouthrinse

Lasting Relief. Table VI presents the lasting dentin hypersensitivity results from two independent and double-blind clinical studies, which compared the 0.8% arginine, PVM/MA copolymer, pyrophosphates, and sodium fluoride mouthrinse to a mouthrinse without a hypersensitivity ingredient.[51,52] During these studies, the subjects brushed at home twice daily with a dentifrice without a sensitivity ingredient for up to eight weeks. After each brushing, subjects immediately rinsed with 20 mL of their mouthrinse for 30 seconds. Use of the arginine mouthrinse provided statistically significant improvements in dentin hypersensitivity after two, four, six, and eight weeks of use, as measured by both the Yeaple Probe and by air blast measurements.

Against Other Technologies. Table VI also presents the results

Table III
Dentin Hypersensitivity Efficacy of 8% Arginine-Calcium Carbonate Dentifrice Against Negative Control Dentifrice

Reference	Investigators	Location	N	2 Weeks*				4 Weeks*				8 Weeks*			
				Yeaple Probe	Air blast	Jay Probe	VAS	Yeaple Probe	Air blast	Jay Probe	VAS	Yeaple Probe	Air blast	Jay Probe	VAS
41	Que, *et al.* 2010	China	81** 81	64.4% 61.0%	40.7% 41.7%			71.1% 67.8%	58.8% 58.2%			61.0% 59.4%	74.4% 77.9%		
42	Docimo, *et al.* 2011	Italy	100	66.9%	28.9%			140.1%	69.8%			146.6%	81.8%		
43	Kakar, *et al.* 2012	India	74	81.9%	39.5%			90.5%	56.7%			116.7%	76.7%		
44	Kakar, *et al.* 2013	India	93	63.4%	30.5%	74.2%	25.8%	110.4%	51.7%	121.0%	46.7%	152.2%	78.8%	155.5%	71.1%
45	Hegde, *et al.* 2013	India	86	—	55.6%	67.4%	41.5%	—	67.5%	108.6%	56.7%	—	82.1%	139.6%	72.2%
		Mean		67.5%	39.5%			95.9%	60.4%			107.2%	78.6%		
		Range		61.0% - 81.9%	30.5% - 55.6%			67.8% - 140.1%	51.7% - 69.8%			59.4% - 152.2%	74.4% - 82.1%		

* Percentage change calculated as the mean of the 8% arginine-calcium carbonate dentifrice relative to the mean of the negative control dentifrice at each time point. A positive value indicates an improvement for the 8% arginine-calcium carbonate dentifrice relative to the negative control dentifrice.
**Contains high-cleaning calcium carbonate

Table IV
Immediate Dentin Hypersensitivity Efficacy of 8% Arginine-Calcium Carbonate Dentifrice Against Alternative Technologies

Reference	Investigators	Location	N	Immediate*		3 Day*		7 Day*	
				Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast
36	Ayad, *et al.* 2009	Canada	80[1]	130.7%	43.8%	104.9%	44.5%		
37	Nathoo, *et al.* 2009	New Jersey	83[1]	161.2%	59.8%	147.1%	70.1%		
39	Li, *et al.* 2011	California	100[2]	80.5%	41.4%			32.1%	50.4%

* Percentage change calculated as the mean of the 8% arginine-calcium carbonate dentifrice relative to the mean of the dentifrice using an alternative technology at each time point. A positive value indicates an improvement for the 8% arginine-calcium carbonate dentifrice relative to the dentifrice using an alternative technology.
[1] Dentifrice with 5% Potassium Nitrate (Colgate Sensitive; Colgate-Palmolive Company)
[2] Dentifrice with 8% Strontium Acetate (Sensodyne Rapid Relief; GlaxoSmithKline)

Table V

Dentin Hypersensitivity Efficacy of 8% Arginine-Calcium Carbonate Dentifrice Against Alternative Technologies

Reference	Investigators	Location	N	3 Day*		7 Day*		2 Weeks*		4 Weeks*		8 Weeks*	
				Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast
46	Ayad, *et al.* 2009	Canada	77[1]	0.0%**	0.8%**			16.2%	16.2%	22.4%	29.2%	21.4%	63.4%
47	Docimo, *et al.* 2009	Italy	80[1]					37.0%	23.9%	30.0%	32.0%	12.2%	29.3%
48	Docimo, *et al.* 2009	Italy	80[2]			28.9%	3.4%**	38.9%	16.8%	28.9%	26.4%	11.6%	33.8%
42	Docimo, *et al.* 2011	Italy	100[3]					41.7%	24.9%	52.3%	58.3%	28.4%	60.7%
49	Schiff, *et al.* 2011	California	121[3]									51.3%	39.4%
50	Kakar, *et al.* 2012	India	88[4]					36.2%	16.4%	33.1%	31.1%	29.7%	58.8%

*Percentage change calculated as the mean of the 8% arginine-calcium carbonate dentifrice relative to the mean of dentifrice using an alternative technology at each time point. A positive value indicates an improvement for the 8% arginine-calcium carbonate dentifrice relative to the dentifrice using an alternative technology.

** Indicates no significant difference ($p > 0.05$) between the 8% arginine/calcium carbonate dentifrice and the dentifrice with potassium ion

[1] Dentifrice with 2% potassium ion as 3.75% potassium chloride (Sensodyne Total Care F, GlaxoSmithKline)

[2] Dentifrice with 2% potassium ion as 5% potassium nitrate (Sensodyne Total Care Gentle Whitening, GlaxoSmithKline)

[3] Dentifrice with 8% strontium acetate (Sensodyne Rapid Relief, GlaxoSmithKline)

[4] Dentifrice with 2% potassium ion as 5% potassium nitrate (Sensodyne Fresh Mint, GlaxoSmithKline)

Table VI

Dentin Hypersensitivity Efficacy of 0.8% Arginine, PVM/MA Copolymer, Pyrophosphate Mouthrinse Against Other Mouthrinses

Reference	Investigators	Location	N	2 Weeks*		4 Weeks*		6 Weeks*		8 Weeks*	
				Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast
51	Hu, *et al.* 2013	China	90[1]	22.1%	14.2%	37.1%	24.1%			44.6%	24.0%
52	Elias Boneta, *et al.* 2013	Dominican	43[1]	125.3%	51.2%	172.9%	76.6%	232.6%	80.4%		
		Republic	48[2]	86.3%	37.6%	100.7%	65.9%	86.2%	68.2%		

* Percentage change calculated as the mean of the 0.8% arginine, PVM/MA copolymer, pyrophosphate mouthrinse relative to the mean of other mouthrinses at each time point. A positive value indicates an improvement for the 0.8% arginine, PVM/MA copolymer, pyrophosphate mouthrinse relative to other mouthrinses.

[1] Mouthwash with no sensitivity ingredient

[2] Mouthwash with 2.4% potassium nitrate

of one study in which the dentin hypersensitivity efficacy of the 0.8% arginine, PVM/MA, pyrophosphates, sodium fluoride mouthrinse was compared to a competitive mouthrinse containing 2.4% potassium nitrate as the active ingredient.[52] In this study, in which the efficacy was determined after two, four, and six weeks of product use, the 0.8% arginine, PVM/MA, pyrophosphates, sodium fluoride mouthrinse provided superior dentin hypersensitivity efficacy measured by both the Yeaple Probe and the air blast technique.

Overall Conclusion from Two Clinical Efficacy Studies on Dentin Hypersensitivity with a 0.8% Arginine/PVM/MA Copolymer/Pyrophosphate Mouthrinse

The overall conclusion from the two independent clinical efficacy studies shown in Table VI is that a mouthrinse containing 0.8% arginine, PVM/MA copolymer, and pyrophosphates provides a significant and clinically meaningful reduction of dentin hypersensitivity, after up to eight weeks of product use as compared to the similar use of a negative control mouthrinse and to a mouthrinse containing potassium nitrate.

Regimen

In-Office Desensitizing Paste + Dentifrice. Table VII presents the results of a clinical study in which subjects were treated with the 8% arginine and calcium carbonate desensitizing paste in-office, and were instructed to brush twice daily at home for the next 24 weeks using an 8% arginine, calcium carbonate, and SMFP dentifrice.[1] Subjects returned for follow-up measurements after eight and 24 weeks. At each time point, the dentin hypersensitivity benefit observed immediately after application of the desensitizing paste was maintained through at-home use of the 8% arginine, calcium carbonate, and SMFP dentifrice. In another clinical regimen, in one group of patients (Test), the 8% arginine and calcium carbonate desensitizing paste was applied to chronic periodontitis patients following non-surgical periodontal treatment and before flap closure. Additionally, patients were requested to brush with the 8% arginine, calcium carbonate, and SMFP dentifrice over the next 17 weeks.[53] The other group (Control) received a fluoride-free, non-desensitizing pumice paste for the in-office part of the treatment, and brushed at home with a regular fluoride dentifrice without a desensitizing agent. The results of the study indicated that the VAS scores in the Test group decreased at eight, 11, and 17 weeks after treatment. There was also a decrease in air blast (Schiff) scores at eight and 11 weeks. The VAS and air blast scores increased for users in the Control group, and there were statistically significant differences between the groups at all time points after baseline.

Dentifrice + Mouthrinse. Table VII also presents the results of a more traditional at-home regimen, during which one group of subjects brushed twice daily with an 8% arginine, calcium carbonate, and SMFP dentifrice, and then rinsed with an 0.8% arginine,

Table VII
Dentin Hypersensitivity Efficacy of Arginine-Based Regimens

Reference	Investigators	Location	N	Immediate (in office only)*		2 Weeks*		4 Weeks*		8 Weeks*		24 Weeks*	
				Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast	Yeaple Probe	Air blast
1	Hamlin, *et al.* 2012	Pennsylvania	95[1]	49.8%	26.0%					57.5%	38.4%	32.9%	34.3%
54	Elias Boneta, *et al.* 2013	Dominican Republic	78[2]			92.5%	44.4%	121%	58.5%	135.7%	70.2%		
			80[3]			61.2%	32.4%	54.5%	32.8%	68.6%	49.6%		

* Percentage change calculated as the mean of the arginine-based regimen relative to the mean of another regimen at each time point. A positive value indicates an improvement for the arginine-based regimen relative to another regimen.
[1] 8% arginine/calcium carbonate desensitizing paste + 8% arginine/calcium carbonate/fluoride dentifrice as compared to pumice-based prophylaxis paste + non-desensitizing fluoride dentifrice
[2] 8% arginine/calcium carbonate/fluoride dentifrice + 0.8% arginine, PVM/MA copolymer, pyrophosphates, fluoride mouthrinse as compared to a non-desensitizing fluoride dentifrice + non-desensitizing mouthrinse
[3] 8% arginine/calcium carbonate/fluoride dentifrice + 0.8% arginine, PVM/MA copolymer, pyrophosphates, fluoride mouthrinse as compared to a 5% potassium nitrate/fluoride dentifrice + 0.51% potassium chloride/fluoride mouthrinse

PVM/MA copolymer, pyrophosphate, sodium fluoride mouthrinse for eight weeks. The results of this study show that this regimen provides superior dentin hypersensitivity efficacy to a negative control regimen comprised of a non-desensitizing dentifrice and mouthrinse, as well as superiority to a regimen using a potassium-based dentifrice and potassium-based mouthrinse.[54]

Overall Conclusion from Two Clinical Efficacy Studies on Dentin Hypersensitivity with an Arginine-based Regimen

The overall conclusion from the two independent clinical efficacy studies shown in Table VII is that arginine-based regimens provide significant and clinically meaningful reductions of dentin hypersensitivity as compared to the similar use of a negative control regimen or a regimen based on potassium salts.

Other Endpoints

Erosion

Dissolution of enamel and dentin by acidic challenges can result in erosion. Previous research established that a dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP provided protection from enamel erosion.[15,16,18]

Rege, *et al.* took this research a step further by first exposing the enamel to citric acid and producing a roughened surface.[55] Application of the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP coated the surface and reduced the appearance of surface roughening as observed with SEM. Using ESCA, the presence of nitrogen from arginine was identified, while SIMS confirmed arginine's presence using its signature peaks at 112 amu and 175 amu.

In a clinical study, Sullivan, *et al.* employed a double-blind, cross-over design and an intra-oral erosion model to investigate the ability of the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP to reduce further demineralization of eroded enamel.[56] Subjects wore an upper palatal appliance containing three demineralized bovine enamel samples for 24 hours per day, with the exception of meal times. The study was conducted in two phases, with each phase lasting five days. In each of the phases, subjects used either a silica-based dentifrice containing 1450 ppm fluoride as SMFP, or the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP. The subjects brushed their teeth (but not the enamel samples) morning and evening with the allocated dentifrice for one minute, and this was followed by swilling the slurry around the mouth for one minute and then rinsing with 15 ml of water. Four challenges per day with 1% citric acid occurred to simulate an erosive challenge. Changes in mineral content were monitored using Quantitative Light-induced Fluorescence (QLF). There was a smaller mineral loss from the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP (9.74%) as compared to the silica-based dentifrice containing 1450 ppm fluoride as SMFP (18.36%), indicating better protection against erosion for the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP.

In a second clinical study, Sullivan, *et al.* used a similar design, but modified the conditions to favor remineralization of the samples rather than demineralization as in the first study.[57] Changes in mineral content were measured using a Knoop microhardness tester before and after treatment. When subjects used the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP, the hardness increased by 14.99%, which was statistically significantly ($p < 0.05$) greater than the 8.66% when a dentifrice containing 1450 ppm fluoride as SMFP was used.

The results of these studies suggest that, in addition to depositing on the dentin, the dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP helps protect the enamel from further erosion and also remineralizes eroded enamel.

Stain Removal

Table VIII presents the results of an eight-week clinical study using a high-cleaning calcium carbonate in the 8% arginine dentifrice in order to assess its ability to remove extrinsic stains.[58] Using the method described by Lobene, each tooth was scored independently using a four-point stain area scale and a four-point stain intensity scale.[59] There were no differences between the two treatment groups at baseline for either the evaluated area or intensity stain parameters. After four weeks and eight weeks of use, subjects brushing with the 8% arginine dentifrice with the high-cleaning calcium carbonate demonstrated significant improvements in stain removal as compared to the control dentifrice. Relative to the control dentifrice, the 8% arginine, high-cleaning calcium carbonate, fluoride dentifrice demonstrated reductions in mean stain intensity scores of 9.7%

Table VIII
Whitening Efficacy
8% Arginine, High-cleaning Calcium Carbonate, Fluoride Dentifrice

Reference	Investigators	Location	N	4 Week*		8 Week*	
				Stain Area	Stain Intensity	Stain Area	Stain Intensity
58	Yin, *et al.* 2010	China	92	11.7%	9.7%	20.8%	17.9%

* Percentage change calculated as the mean of the 8% arginine-calcium carbonate dentifrice with high cleaning calcium carbonate relative to the mean of the control dentifrice at each time point. A positive value indicates an improvement for the 8% arginine-calcium carbonate dentifrice with high cleaning calcium carbonate relative to the control dentifrice.

and 17.9% at the four-week and eight-week evaluations, respectively. Corresponding reductions in mean stain area scores for the 8% arginine, high-cleaning calcium carbonate, and fluoride dentifrice relative to the control dentifrice were 11.7% and 20.8% at the four-week and eight-week evaluations, respectively. All reductions were statistically significant ($p < 0.05$).

Calculus and Gingivitis

Li, *et al*. investigated whether six months' use of a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP would increase the amount of supragingival calculus formation, and if any changes in gingival index would be observed as compared to a dentifrice containing 1450 ppm fluoride as SMFP.[60] After three and six months, there were no significant differences between the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP and the dentifrice containing 1450 ppm fluoride as SMFP with respect to the amount of calculus as measured using the Volpe-Manhold Index.[61] In addition, there were no statistically significant differences between the two dentifrices with respect to their impact on gingivitis after three and six months of product use.

Malodor

Hu, *et al*. investigated whether six months' use of a dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm fluoride as SMFP would result in an increase in oral malodor potentially associated with increased ammonia production from the breakdown of arginine, as compared to a commercial dentifrice with 1450 ppm fluoride as SMFP.[62] A panel of four expert judges used a nine-point hedonic scale to evaluate breath odor. Before breath odor evaluations, subjects refrained from eating odorigenic foods for 48 hours and did not use dental hygiene procedures, breath mints, or mouthrinses for 12 hours. There was no statistically significant ($p > 0.05$) difference in the effects of the two dentifrices on oral malodor levels. Thus, the presence of arginine, which has been shown to increase ammonia production, did not cause a concomitant increase in oral malodor.

Shear Dentin Bond Strength

In-Office. Three studies evaluated the effect of the 8% arginine and calcium carbonate desensitizing paste on dentin bonding of self-etch adhesives.[63-65] In the first study, intact human premolars were extracted, the occlusal enamel was removed, and dentin slices were polished.[63] After etching with 1% citric acid, samples were either left untreated, polished with silicon dioxide for 30 seconds, or treated with the 8% arginine and calcium carbonate desensitizing paste for either six, 18, or 30 seconds. The samples were treated with a one-step self-adhesive (G-Bond [GC Corporation, Tokyo, Japan] or FI-Bond II [Shofu Inc., Kyoto, Japan]) according to the manufacturers' directions, and microtensile bond strength was determined. In the second study, extracted human third molars were sectioned to expose mid-coronal dentin and ground with silicon carbide paper to create a standard surface.[64] After exposure to a 1% citric acid solution, the samples were treated with one of three dentin desensitizers (8% arginine-calcium carbonate desensitizing paste, a casein phosphopeptide–amorphous calcium phosphate (CPP-ACP)-containing paste, an experimental hydroxyapatite paste) or left untreated. Afterward, the samples were treated with a one-step self-etch adhesive (G-Bond or Clearfil S[3] [Kuraray Medical, Okayama, Japan]) according to manufacturers' directions and microtensile bond strength was determined. In study three, intact human premolars were extracted and either used without treatment, used after treatment with a polishing paste, or used after treatment with the 8% arginine-calcium carbonate desensitizing paste.[65] Microtensile bond strength was determined after treatment with one of two self-etching adhesives (G-Bond or FI-Bond II). The results from the three studies are shown in Figures 13-15. The 8% arginine-calcium carbonate desensitizing paste provides an increase in bond strength for the G-Bond self-adhesive, whereas there was no change in bond strength for the other test products. Furthermore, this bond strength increases with application time. In addition, there was no adverse effect of the 8% arginine-calcium carbonate desensitizing paste on bond strength with either the FI-Bond II or the Clearfil-S[3] self-etch adhesives.

One study evaluated the effect of the 8% arginine-calcium carbonate desensitizing paste on enamel bonding of resin composites.[66] In this study, buccal and lingual surfaces from extracted human molars were polished with either pumice or the 8% arginine-calcium carbonate desensitizing paste to create a uniform flat surface area to which one of two resin composites (Filtek Supreme [3M ESPE, St. Paul, MN, USA] or Premise [Kerr Corporation, Orange, CA, USA]) was bonded according to the manufacturers' instructions. After 48 hours, the microtensile bond strength was determined, which showed that there was no impact on the enamel bonding of these resin composites (Figure 16).

Dentifrice. Canares, *et al.* determined the effect of an 8.0% arginine and calcium carbonate desensitizing dentifrice on shear dentin bond strength.[67] Mean shear force was 19.6 ± 9.4 (SD) for the experimental group and 15.4 ± 6.0 for the control group, with $p = 0.0291$. No significant differences were found for bond strength to dentin treated with an 8.0% arginine-calcium carbonate desensitizing dentifrice or pumice.

Surface Roughness. Garcia-Godoy, *et al.* evaluated the effect of an 8% arginine-calcium carbonate desensitizing paste on the surface roughness of resin composite, porcelain, amalgam, gold, and human enamel.[68] Roughness was evaluated using both 3D non-contact and

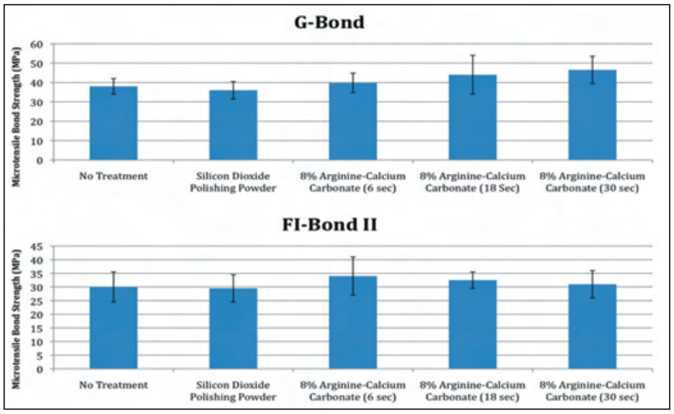

Figure 13. *Effect of treatment time on bond strength of two self-etch adhesives.*

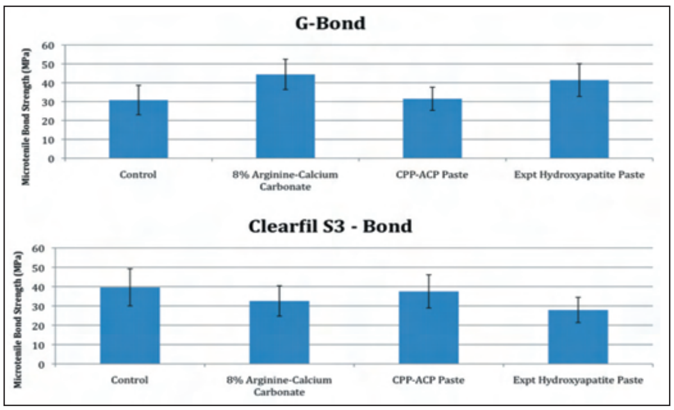

Figure 14. *Effect of in-office paste on self-etch adhesives.*

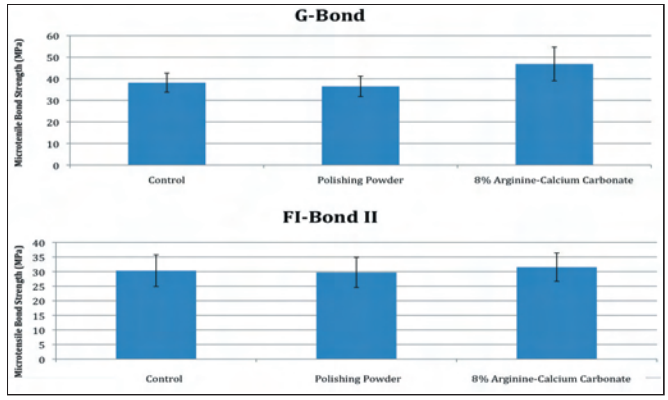

Figure 15. *Effect of in-office paste on self-etch adhesives.*

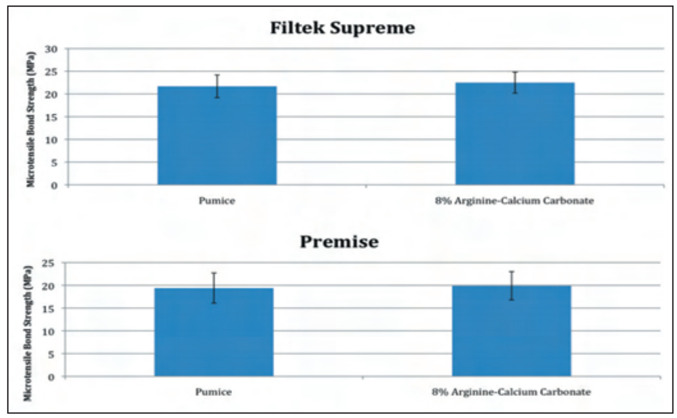

Figure 16. *Effect of in-office paste on bond strength of resin composites.*

stylus profilometers. The 8% arginine-calcium carbonate desensitizing paste was applied to each surface for 15 seconds using a single disposable prophy cup. Results indicate that the 8% arginine-calcium carbonate desensitizing paste did not have a significant effect on the surface roughness of the substrates tested.

Summary

Clinical and laboratory studies clearly indicate that the use of oral care products with the arginine provide dentin hypersensitivity relief compared to products without a desensitizing agent, as well as to those that use alternative agents. Studies summarized in this Supplement have demonstrated that these products provide not only immediate relief, but lasting relief as well from dentin hypersensitivity. Dental professionals can recommend these products with confidence for their patients who need relief from dentin hypersensitivity.

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Supplemental Readings

a. Panagakos F, Schiff T, Guignon A. Dentin hypersensitivity: Effective treatment with an in-office desensitizing paste containing 8% arginine and calcium carbonate. *Am J Dent* 2009;22(Spec Iss A):3A-7.
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Notes

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