AlkaGen Technology™

Breakthrough technology that mimics saliva's profound benefits in helping maintain healthy teeth

There is compelling evidence that alkali generation by bacteria on tooth surfaces can have significant benefits in maintaining healthy teeth. More than 100 years ago, Miller identified and described the acid-decalcification theory as a two-step process.[1] In the first step, oral bacteria metabolize fermentable carbohydrates (sugars and starches) to produce acid, which demineralizes tooth tissue in the second step. Researchers recognized the need to develop oral care products that can simultaneously affect the acid production and the enamel remineralization processes. Numerous observations made it evident that saliva was capable of significantly affecting both. Landmark studies by Kleinberg identified that the bacteria in plaque are able to produce base from nitrogenous substrates, which are provided mostly from saliva. The key nitrogenous substrate involved in base formation is arginine. Another important way in which saliva exerts its significant supportive activity is by providing minerals that inhibit demineralization and facilitate remineralization. These discoveries have provided a basis for designing natural ingredients that behave like saliva. This has led to the development of the Alkagen Technology™, which provides a new way of maintaining healthy teeth and supporting a normal pH on tooth surfaces.

The primary source of carbohydrate substrates metabolized by the oral bacteria is the diet. It provides sucrose and other sugars (glucose and fructose) and food starches. Salivary glycoproteins can also provide fermentable carbohydrates, but the amounts are small by comparison. Nonetheless, they may be important in determining the number and in selecting the types of acidogenic bacteria that prevail in the mouth. Studies on pure cultures of oral bacteria have shown that carbohydrate fermentation is mostly carried out by the Gram-positive bacterial component of the oral microflora and far less by the oral Gram-negatives.[2] The latter bacteria, particularly those that are anaerobic, are involved more in putrefaction and periodontal disease.[3]

Studies carried out in the 1940s by Stephan showed that the bacterial communities that grow on poorly accessible surfaces of the teeth as dental plaque are able to rapidly convert sugar substrates to acid and cause the pH of the plaque and underlying tooth surface to rapidly fall.[4] Subsequent studies demonstrated that lactic acid is the dominant acid produced when sugar substrate is in abundance. When less sugar is available, other acids (including acetic, propionic, formic and succinic acids) are observed. An important finding was that restriction in the flow of saliva from the major glands resulted in a lower and more prolonged acidic pH being produced than when the flow of saliva is normal.[5]

Investigators have tried with varying degrees of success to reduce acid production by the microorganisms in dental plaque. This has included methods that tried to reduce the availability of fermentable carbohydrate from the diet, reduce the amount of plaque and acidogenic bacteria in dental plaque, interfere with specific bacteria, and interfere with bacterial glycolysis (the metabolic process by which the plaque bacteria make acid from carbohydrates). It has also included methods that have tried to neutralize the acids formed during glycolysis and have tried instead to stimulate the formation of base by the plaque bacteria to counter acid formation.[6] These methods have had variable degrees of success.

Researchers have had better results in protecting teeth by combating the second step of the Miller process with fluoride. This effect is accomplished mostly by fluoride inhibiting the rate of acid solubilization of the calcium phosphate that constitutes most of the mineral in enamel, cementum, and dentine, and by fluoride favoring remineralization of these tissues.[7]

Early on, dental researchers recognized the need to develop agents that can simultaneously affect the acid production and the enamel remineralization processes. Numerous observations made it evident that saliva was capable of significantly affecting both. Therefore, it was logical to try and understand how this was accomplished, and develop compositions that could do the same thing. Many studies have been directed toward finding the basis of the substantial protective effect of saliva. These have included studies showing that saliva contains buffers (mostly bicarbonate and phosphate) that help neutralize the acids produced by the plaque bacteria.[6]

Landmark studies by Kleinberg identified that the bacteria in plaque are able to produce base from nitrogenous substrates, which are provided mostly from saliva.8 In this way, it becomes possible to raise the pH or counter the pH lowering ability of the plaque when it is producing or has produced acid from fermentable carbohydrate. This led to the concept of plaque being a collection of microbial communities throughout the mouth, each engaged in a common acid-base metabolism.[9]

The key nitrogenous substrates involved in base formation are urea and arginine with saliva as the main intraoral source.[8] They play different roles in base formation, but arginine and the bacteria responsible for their catabolism are the more important elements involved in this process. This is because continual presence of arginine favors selection of acidogenic Gram-positive bacteria that are also arginolytic. Absence of arginine favors their acidogenic nonarginolytic counterparts. Both types of bacteria produce a pH decrease when exposed to sugar substrate, but only those that are arginolytic have the ability to lessen the pH fall and return the pH from acidity to its starting pH condition.[10] Simply stated, arginine is crucial in ecologically favoring more of these bacteria as normal components of the oral microbiota.

Unlike nonarginolytic acidogens, arginolytic acidogens are able to readily produce base from arginine because these bacteria, as part of their enzymic repertoire, contain a series of enzymes that constitute the arginine deiminase pathway.[11] A later study by van Wuyckhuyse, et al, showed that individuals with elevated levels of salivary arginine, have the healthiest, base generating, oral microflora.[12]

pH-raising Activity of Oral Micro-organisms Determined with Arginine or Arginine Peptide

Kleinberg I, A mixed-bacteria ecological approach to understanding the role of oral bacteria in dental caries causation: an alternative to streptococcus mutans and the specific plaque hypothesis. *Crit. Rev. Oral Biol. Med.* 13, 115, 2002.

pH-raising	Non-pH-raising	pH-raising	Non-pH-raising
S. mutans FA-1(b)	*S. mutans* OMZ-61 (a)	*A. naeslundii* ATCC 19039	*A. viscosus* ATCC 15987
BHT (b)	E-49 (a)		
GF-71 (b)	AHT (a)		
130-P (b)		*A. odontolyticus* ATCC 17982	
	S. mutans GS-5 (c)		*A. israelii* ATCC 27037
	10449 (c)		
	Ingbritt (c)		
	S. mutans P-4 (e)	*L. cellobiosus* ATCC 11739	*L. acidophilus* ATCC 4356
	AT-IO (e)	*L. brevis* ATCC 11577	*L. salivarius* ATCC 11741
	LM-7 (e)		
	S. mutans OMZ-175 (f)	*L. fermentum* NCTC 6991	*L. casei* NCTC 6375
	QP50-1 (f)		
	S. mutans ATCC 27353 (d/g)		*N. sicca* ATCC 29256
	OMZ-176 (d/g)		
	B-13 (d/g)		*N. subflava* ATCC 10555
	6715 (d/g)		
S. sanguis G9B (Type A)	*S. sanguis* ATCC 10557 (Type B)		*B. catarrhalis* ATCC 23246
S. milleri	*S. mitior*		
S. faecalis ATCC 4082			

Another important way in which saliva exerts anticaries activity is by providing calcium and phosphate ions to inhibit demineralization by mass action and facilitate remineralization. Many studies have focused on the direct role of these ions in these biological processes, but an indirect and more effective way whereby saliva can provide calcium and phosphate for these mineralization and remineralization purposes was found.

When saliva is secreted into the mouth, several salivary components come together in progressively greater amounts as the pH rises above neutrality. A rapid rise in the pH occurs during saliva stimulation and can reach as high as 8.3.[6] As a result, a complex of glycoprotein and calcium phosphate forms, which readily becomes incorporated into dental plaque. The calcium phosphate is amorphous or poorly crystalline in nature. This complex has been named Salivary Precipitin, and its chemical composition and some of its properties have been determined.[13] One extremely important property is that the calcium phosphate of Salivary Precipitin is very soluble.[13] In fact, it is almost 8 to 10 times more soluble than tooth calcium phosphate. It has also been implicated as a source of ions for remineralization of decalcified tooth tissue and for raising the levels of these ions in plaque fluid to where it can prevent tooth demineralization. The calcium phosphate raises the buffering ability of the plaque, allowing for the neutralization of plaque acids at the same time that its calcium and phosphate ions are rapidly released to remineralize areas of the teeth.

These discoveries have provided a better understanding of the way in which saliva bears upon the Miller process. It has also provided a basis for designing a product that behaves like saliva. This is what has led to the development of Alkagen Technology which contains nutrients that promote healthy intraoral base-forming capability along with an increase in mineralizing ability. The components of the

Alkagen Technology includes arginine, calcium, and anion carriers. Arginine and calcium at the pH of the mouth have a positive charge. They are then able to form salts and salt complexes when combined with negatively charged anions.

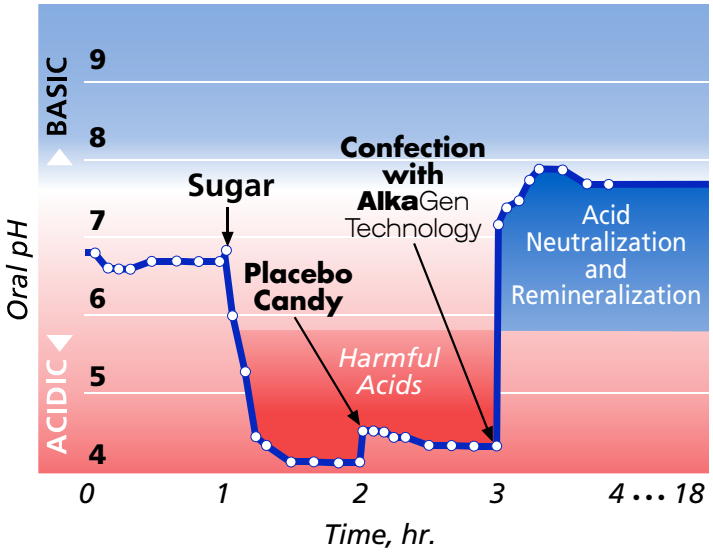
The arginine component of Alkagen Technology favors the formation of base by the dental plaque bacteria to counter acid production. At the same time, the arginine favors the presence of arginolytic over nonarginolytic acidogens, thus the maintenance of a healthier, base producing, plaque microflora. In the mouth, arginine is normally and mainly available from readily degradable peptides and less readily degradable proteins in saliva.

Calcium is also an essential component of Alkagen Technology. It supports tooth enamel by mass action and reduces the release of calcium from tooth mineral when attacked by plaque acids. Calcium precedes the release of phosphate from enamel, dentine, and cementum in an acid producing environment.[14] This means that it is better to use calcium rather than phosphate as a way of maintaining healthy teeth. Additionally, in an optimal neutral or elevated pH, calcium is available to begin the remineralization process and help support the structure of intact enamel.

The bicarbonate/carbonate anions of Alkagen Technology are capable of supporting the activities of calcium and arginine. For example, such anions may provide buffering which enhance the base forming and thereby the acid neutralizing activity of the arginine. Also, these anions can act as a tooth mineral surface covering. If hydrolyzed by the plaque bacteria, the release of phosphate ions will protect the teeth or promote tooth remineralization.

Studies both clinical and in vitro demonstrated that confections containing the Alkagen Technology were effective in neutralizing plaque acids for many hours and were able to help maintain healthy teeth over a one-year period.

In one of several in vitro studies, extracted third molar fissures were filled with different types of oral bacteria isolated from dental plaque. Glucose and arginine bicarbonate/ calcium carbonate, alone or in toothpaste or in a mint confection, were supplied to fissures in various ways and the pH was monitored for up to 18 hours. Acidogenic bacteria gave large pH drops upon glucose exposure. In contrast, adding arginine bicarbonate/calcium carbonate raised the pH immediately to 8.0 and above, where it remained overnight instead of remaining acidic. The confection was ableto keep the pH elevated even when fermentable carbohydrate was subsequently added.[15]



In a one-year, double blind, placebo controlled, clinical study in 10 and 11-year-old children, a confection containing the Alkagen Technology was evaluated for its ability to maintain healthy teeth. Study participants took four mints daily, two in the morning after brushing their teeth and before eating breakfast and two in the evening after brushing their teeth and before going to bed. There were 200 children enrolled in this study of which 195 finished with complete data. Ninety-six of the children were in the study group that received mints containing Alkagen Technology and ninety-nine in the study group that received sugarless placebo mints. The results demonstrated that the children who were administered mints with Alkagen Technology had significantly fewer caries after one year as compared to the children in the placebo group.[16]

There have been numerous clinical trials, which have evaluated the addition of arginine/bicarbonate and calcium carbonate in non-confection products for treating dentinal sensitivity and dental caries. Clinical trials have shown that arginine/bicarbonate and calcium carbonate containing dentifrice products, with and without fluoride, were significantly effective in reducing dentinal sensitivity by plugging and sealing dentinal tubules.[17,18,19] Clinical studies evaluating arginine/bicarbonate and calcium carbonate containing dentifrice products, with and without fluoride, were shown to have significant anti caries benefits.[20, 21,22]

The role of saliva in protecting teeth has become clearer. The Alkagen Technology, which is based on a breakthrough in saliva chemistry and physiology, is an innovative way of helping maintain healthy teeth and supporting a normal pH on tooth sufaces.

References

1. Miller W. Microorganisms of the Human Mouth. Philadelphia, Pa: SS White and Co; 1890.

2. Ryan C, Kleinberg I. A comparative study of glucose and galactose uptake in pure cultures of human oral bacteria, salivary sediment, and dental plaque. *Archs Oral Biol.* 1995;39:743-752.

3. Kleinberg I, Westbay G. Salivary and metabolic factors involved in oral malodor production. *J Periodontol.* 1992;63:768-775.

4. Stephan R. Changes in hydrogen-ion concentration on tooth surfaces and in carious lesions. *JADA.* 1940;27:718-723.

5. Englander H, Shklair I, Fosdick L. The effects of saliva on the pH and lactate concentration in dental plaques in caries-rampant individuals. *J Dent Res.* 1959; 38:848-853.

6. Jenkins G. The Physiology and Biochemistry of the Mouth. 4h ed. Oxford, England: *Blackwell Scientific Publications*; 1978.

7. Ekstrand J. Enhancing effects of fluoride. In: Bowen W, Tabak L, eds. Cariology for the Nineties. Rochester, New York: University of Rochester Press; 1993:409-420.

8. Kleinberg I, Kanapka J, Chatterjee R, et al. Metabolism of nitrogen by the oral mixed bacteria. In: Kleinberg I, Ellison S, Mandel I, eds. Saliva and Dental Caries. New York: Information Retrieval; 1979: 357-377.

9. Kleinberg I, Jenkins G. The pH of plaques in the different areas of the mouth before and after meals and their relationship to the pH and flow of resting saliva. *Archs Oral Biol.* 1964;9:493-516.

10. Wijeyeweera R, Kleinberg I. Acid-base pH curves in vitro with mixtures of pure cultures of human oral microorganisms. *Archs Oral Biol.* 1989;34:55-64.

11. Kanapka J, Kleinberg I. Catabolism of arginine by the mixed bacteria in human salivary sediment under conditions of low and high glucose concentration. *Archs Oral Biol.* 1983;28:1007-1015.

12. van Wuyckhuyse B, Perinpanayagam H, Bevacqua D, et al. Association of free arginine and lysine concentrations in human parotid saliva with caries experience. *J Dent Res.* 1995;74:686-690.

13. Kleinberg I, A mixed-bacteria ecological approach to understanding the role of oral bacteria in dental caries causation: an alternative to streptococcus mutans and the specific plaque hypothesis. *Crit. Rev. Oral Biol. Med.* 13, 108-125, 2002.

14. Gray J, Francis M, Griebstein W. Chemistry of enamel dissolution. In: Sognnaes R, ed. Chemistry and Prevention of Dental Caries. Springfield, Illinois: Charles Thomas; 1962:164-179.

15. Chatterjee R, Kleinberg I. Bacterial acidification and Cavistat alkalinization of occlusal fissure pH. CD-ROM of Abstracts. *J. Dent. Res.*, Special Issue A., 84: 3264, 2005.

16. Acevedo AM, Montero M, Rojas-Sanchez F, Machado C, Rivera LE, Wolff M, and Kleinberg I. Clinical evaluation of the abilityof CaviStat in a mint confection to inhibit the development of dental caries in children. *J Dent Res.* 19: 1-8, 2008.

17.Schiff T, Mateo LR, Delgado E, Cummins D, Zhang YP, DeVizio W. Clinical efficacy in reducing dentin hypersensitivity of a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride compared to a dentifrice containing 8% strontium acetate and 1040 ppm fluoride under consumer usage conditions before and after switch-over. *J Clin Dent.* 2011;22(4):128-38.

18. Schiff T, Delgado E, Zhang YP, Cummins D, DeVizio W, Mateo LR. Clinical evaluation of the efficacy of an in-office desensitizing paste containing 8% arginine and calcium carbonate in providing instant and lasting relief of dentin hypersensitivity. *Am J Dent.* 2009 Mar;22 Spec No A:8A-15A.

19. Petrou I, Heu R, Stranick M, Lavender S, Zaidel L, Cummins D, Sullivan RJ, Hsueh C, Gimzewski JK. A breakthrough therapy for dentin hypersensitivity: how dental products containing 8% arginine and calcium carbonate work to deliver effective relief of sensitive teeth. *J ClinDent.* 2009;20(1):23-31.

20. Kraivaphan P, Amornchat C, Triratana T, Mateo LR, Ellwood R, Cummins D, et al. Two-year caries clinical study of the efficacy of novel dentifrices containing 1.5% arginine, an insoluble calcium compound, and 1450ppm fluoride. *Caries Research.* 2013;10,1159/000353183

21. Souza MLR, Cury JA, Tenuta LMA, Zhang YP, Mateo LR, Cummins D, et al. Comparing the efficacy of a dentifrice containing 1.5% arginine and 1450 ppm fluoride to a dentifrice containing fluoride alone in the management of primary root caries. *Journal of Dentistry.* 2013;41S:35–41

22. Acevedo AM, Machedo C, Rivera LE, Wolff M, Kleinberg I. The inhibitory effect of an arginine bicarbonate/calcium carbonate Cavistat-containing dentifrice on the development of dental caries in Venezuelan school children. *Journal of Clinical Dentistry.* 2005;16:63–70