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Role of Arginine in Caries Prevention

Research Article

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Abstract

Caries is one of the most prevalent oral diseases. The disease arises as the result of a complex interaction of multiple factors. Tooth surfaces are covered with a thin biofilm to which bacteria adhere and mature which utilize dietary sugars as a substrate, producing acid, mainly lactic acid. Bacterial activity causes a decrease in pH, which ultimately causes the hydroxyapatite crystals in the enamel to dissolve. Arginine is a naturally occuring semi-essential amino acid in food products and in the saliva. It is metabolized by arginolytic bacteria which produce ammonia and leads to an increase in the pH in the oral biofilm. This thereby counteracts the acidic environment conducive to the growth of acid-resistant bacteria. The continued research into oral arginine metabolism as a successful approach to caries intervention has been supported by compelling in vitro and in vivo evidence.

Keywords: Caries; Arginine; Caries Prevention; Review.

Introduction

As defined[1], dental caries is a biofilm-mediated, diet-modulated, multifactorial, non-communicable, complex disease that causes net mineral loss in the hard tissues of the teeth. [2,3]. Biological, behavioural, psychosocial, and environmental factors all influence the development of carious lesion.[4] Although the hard tissue shows signs of demineralization, the caries process starts in a bacterial biofilm that is close to the tooth. It's a multifactorial disease that begins with microbiological changes inside a complex biofilm and is influenced by salivary flow and composition, fluoride intake, sugar consumption, and preventive behaviours.[5]

The process starts when acid-producing organisms inside the plaque biofilm, such as mutans streptococci, which metabolise these dietary sugars to create lactic and other acids, causing initial de-mineralization, or the removal of calcium and phosphate ions from the hydroxyapatite structure of the tooth's enamel. This is followed by a reversible early caries lesion that can be remineralized. Fluoride works by encouraging de-mineralized tissue to remineralize.[6-8] Continuous acidification of oral biofilms due to acids formed by bacterial glycolysis of dietary carbohydrates, leads to a rise in the proportions of acid-producing and acid-tolerant species, a selective mechanism that disrupts dental plaque pH homeostasis and changes the demineralization-remineralization balance in favour of mineral loss.[9,10] Importantly, this recent understanding has prompted a shift in clinical dentistry from an emphasis on cavity restoration to the investigation of therapeutic methods to stop or reverse the caries process by re-mineralizing non-cavitated initial enamel or root caries lesions.

The incidence of dental caries is high in most developing low-income countries, and over 90% of caries go untreated.[5] According to the recent Global Burden of Disease survey, untreated caries in permanent teeth is still the most prevalent human disease worldwide.[11] Despite the fact that dental diseases have a low mortality rate, they have a significant effect on eating capacity, diet, and wellbeing in both children and adults. Teeth, in today's culture, play a critical role in improving facial appearance, which has a significant impact on an individual's identity, self-esteem, and trust. As a result, since dental diseases have bad repercussions for people of all ages, proactive measures to avoid them should be taken.

Caries prevention comprises primary and secondary caries prevention. Primary prevention measures include those taken to pre-

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vent the initial dissolution of dental enamel as well as those to halt the progression of early lesions (areas of demineralized enamel) that have not yet progressed to cavitation (secondary caries prevention) During the past decade, multiple new approaches in the management of dental caries have been identified and validated. These include various preventive strategies and recently developed agents such as arginine. Arginine was initially used as an desensitizing agent and only recently has been introduced as an additive in dentifrices with fluoride for caries prevention.

Arginine is a prebiotic, semi essential or conditionally essential amino acid that has a wide range of metabolic applications[12]. It can be produced by the body and secreted in saliva as salivary peptide or in free form .i.e.,endogenous (protein turnover and de novo arginine synthesis from citrulline) or the source could be exogenous i.e. through diet. (Morris 2006) It is metabolized by arginolytic bacteria through an arginine deiminase pathway (ADS) which produce ammonia-like substances [13], this leads to an increase in the pH in the oral biofilm [14] As a result, the acidic condition that encourages the growth of acid-resistant bacteria is reduced.

Previously our team has a rich experience in working on various research projects across multiple disciplines[15-29] Now the growing trend in this area motivated us to pursue this project.

Mechanism Of Action

Diet and salivary peptides are the main sources of arginine for plaque bacteria. Arginine in free form is secreted in saliva at concentrations of about 50 μM[30], and free arginine is present at about 200 μM in mature 48-h dental plaque.[31] Most of the arginine that enters the body through foods, or salivary and other host secretions, is in peptide or protein form. The arginine can then be released into a form that can be internalised and catabolized by abundant ADS-positive bacteria by a variety of proteases formed by the oral microbiota. Plaque bacteria catabolize arginine primarily via the three enzyme ADS, which first transforms arginine to citrulline and ammonia through the enzyme arginine deiminase (AD). A catabolic ornithine transcarbamylase (cOTC) reacts with the citrulline to release ornithine and carbamyl phosphate. A catabolic carbamate kinase (cCK) breaks down carbamyl phosphate to ammonia and CO2 while also donating the phosphate to ADP, resulting in ATP production.[32,33]

Ammonia synthesis through the ADS raises cytoplasmic and environmental pH, which benefits oral bacteria by:

1) shielding them from acid killing[32][34];
2) providing bioenergetic benefits such as increasing pH and synthesising ATP[32] [33]; and
3) maintaining a relatively neutral environmental pH that is less beneficial for cariogenic microflora outgrowth.[32] [35]

Stephan [36] was the first to explain the causal relationship between bacterial sugar metabolism and acid production by a mixed population of plaque bacteria, as well as the fact that the initial decrease in plaque pH is accompanied by a steady increase in plaque pH that gradually reaches a plateau. It was later discovered that the plateau/resting pH of caries-active plaque was more acidic than that of caries-free plaque [37], confirming the connection between acid production and development of caries. Further studies revealed that ammonia production from arginine or urea by a group of bacteria in saliva and plaque is linked to an increase in plaque pH.[13]

Plaque pH can be determined by plaque organisms' acid–base metabolism, which could be influenced by plaque thickness, the quantity of acid-producing and alkali-producing organisms, and the relative availability of nitrogenous and carbohydrate substrates in plaque, according to Kleinberg [38] . In accordance to data from a recent in vitro study, caries development may be affected by the relative rates of acid and base formation in plaque, which are critically dependent on the presence of sucrose, plaque pH and buffer ability, and biofilm age [14].

Free arginine levels in saliva of caries-free people were found to be substantially higher than in saliva of caries patients[30] This explains why dental plaques from caries-free people who have fasted have higher ammonia levels[39,40] and pH values than plaque from caries-active people [39][40][41]. Therefore, differences in arginolysis between caries-free and caries-active people can be attributed to:

1) the strains in oral biofilms with intrinsic differences in the regulation of the ADS by environmental factors; and/or
2) host and biofilm microenvironmental factors that influence ADS expression/activity.

The microenvironment in caries-active individuals' biofilms, for example, may not be conducive to high ADS expression or may contain inhibitory factors that reduce ADS expression or enzyme activity.[42]

Arginine Formulations

Kleinberg in 1999 designed a technology to deliver arginine for plaque bacteria in the mouth through toothpastes, mints, and chews. Over the decade, many clinical trials have been conducted to test this arginine technology with or without combination with fluoride, as arginine has a synergistic effect with it. [42] Daily use of 2% arginine in NaF toothpaste, in high-risk patients, provides a synergistic anti-caries effect given the proven prebiotic benefits of arginine in caries prevention and the demonstrated remineralization effect. [43] CaviStat® (Ortek Therapeutics, Inc., Roslyn, NY, USA) - an arginine bicarbonate-calcium carbonate complex added to a sugarless mint confection was introduced as BasicMints®. Other formulations include incorporation of arginine in toothpastes with various concentrations of fluorides, in mouth rinses,in dental adhesives and gums for easy administration.

Evidence Regarding Anti-Caries Effect Of Arginine

Caries-preventive effect of arginine in various forms such as L-arginine, arginine sugarless confectionery, arginine bicarbonate mouth rinse , arginine non-fluoridated toothpaste, 1.5% arginine-fluoride/fluoride-free toothpaste ,8% arginine-fluoride toothpaste , L-Arg.HCl in NaF toothpaste, L-arginine adhesive, and arginine varnish have been studied by various authors. In vitro studies regarding L-Arginine found it to be effective in maintaining the healthy oral biofilms by improving pH homeostasis through remodeling of the oral microbial flora and reduced the

biofilm biomass.[44][45]

Colgate Maximum Cavity Protection PLUS Sugar Acid Neutralizer toothpaste(1.5% arginine,insoluble calcium base, 1450-ppm NaMFP) was investigated.The fluoride uptake potential of 1.5% arginine-fluoride toothpaste was slightly lower, in an in vitro setting, than the combined 1500 ppm NaF and 1000 ppm NaMFP toothpaste.[46]

Another in vitro research found that 8% arginine toothpaste had significantly higher remineralization ability than casein phosphopeptide amorphous calcium phosphate mousse and 1400 ppm NaF solution.[47,48] Given the known prebiotic benefits of arginine and the demonstrated remineralization effect with micro-CT and increased fluoride absorption, one study concluded that incorporating 2% L- Arg.HCl in NaF toothpaste could provide a synergistic anti-caries effect. But this formulation is not yet available on the market.[43] For secondary caries prevention, arginine (5%, 7%, and 10%) has been incorporated in a two-step etch-and-rinse adhesive, but these formulations are not commercially available. In vitro tests revealed that adding 7% L-arginine to adhesives did not change their mechanical properties but had significant antibacterial effects. [49]

When compared to children who obtained a sugarless mint control, children who used BasicMints®(Cavistat) (4 mints a day) had 52.4 percent fewer non-cavitated caries lesions in the first permanent molars, as well as less carious lesions in primary molars and some early erupting premolars at 12-month follow-up.41 When comparing the caries-preventive capacity of 2 percent arginine bicarbonate mouth rinse to 1 percent urea and/or 0.05 percent NaF solution, researchers discovered that arginine rinsing offered only a minor advantage in terms of remineralization.[50]Another study's authors suggest that arginine bicarbonate mouthrinse (0.5–2%) may be a potential caries-prevention agent, particularly for high-risk patients after carbohydrate intake.[51] As a result, more research is required to support these conflicting findings.

A customised arginine-based sustained-release varnish was made by embedding 3% arginine in an adjusted ethyl cellulose polymer matrix which formed a self-degradable thin film on teeth. The use of arginine varnish as an adjunct to oral hygiene interventions in high-risk patients may be beneficial.[52] A clinical trial using 1.5 % arginine fluoride-free toothpaste revealed a change in bacterial composition toward a healthy culture close to that seen in caries-free people[53,54]. Arginine-fluoride dentifrices were found to have superior caries-preventive efficacy as compared to matched control fluoride dentifrices in many clinical trials. [55,56][53,55] [54,57][55,58] and systematic reviews [59-61][62].

Our institution is passionate about high quality evidence based research and has excelled in various fields [19, 63-72]

Conclusion

Multiple studies have found results supporting use of arginine in various formulations, but these should be considered with caution due to high risk of bias and chances of industrial or publication bias as many studies were funded by the companies.To assess the caries-preventive potential of arginine in commercial formulations, high-quality clinical trials are needed. By integrating L-arginine into self-applied and professionally applied caries-preventive agents, its function in caries prevention can be further investigated.

Disclosure

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Author Contributorship

Astha Bramhecha, contributed to conception, design and concise drafting of the manuscript. Jogikalmat Krithkadatta critically revised the manuscript. The authors give final approval and agrees to be accountable for all aspects of the work.

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