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A Broad Review On Arginine And Its Application In Dentistry

Dr. AntarikshyaPrabir Das[1], Dr. Swadheena Patro[2],Dr. Ankita Mohanty[3], Dr Sanjay Miglani[4]

[1]Post graduate trainee, Dept. of Conservative dentistry and Endodontics, Kalinga institute of dental sciences, KIIT Deemed to be University, BBSR [2]MDS, Professor, Dept of Conservative dentistry and Endodontics, Kalinga institute of dental sciences, KIIT Deemed to be University, BBSR.
[3]Post graduate trainee, Dept. of Conservative dentistry and Endodontics, Kalinga institute of dental sciences, KIIT Deemed to be University, BBSR.

[4]Professor, Department of Conservative Dentistry & Endodontics, Faculty of Dentistry, JamiaMilliaIslamia (A Central University) New Delhi 110025, India

Email ID: [1]drantarikshyadas@gmail.com, [2]drswadheenapatro@gmail.com , [3]ankitamohanty094@gmail.com , [4]smiglani@jmi.ac.in

ABSTRACT: Global data suggest Dental caries is a dysbiotic, biofilm-mediated disease imparting serious health problems impacting almost half the world population. An ecological equilibrium of microbes is crucial for maintaining the human biofilm in a healthy state. One way to restore this homeostasis is to equilibrate the acidity and alkalinity processes to maintain a neutral pH. Physiological factors that can countervail the acidification of biofilms mainly include the buffering capacity of saliva and the metabolism of salivary substrates, such as urea and arginine, which generates alkali in the form of ammonia. Hence, there has been an increasing interest in therapeutic interventions that modulate the microbiome of biofilms to reinstate this balance. The current scenario focuses on approaches using either antimicrobial strategies or to augment the growth of health-promoting bacteria.
Here we review, the knowledge gained from laboratory and clinical studies that support a remarkable role of arginine metabolism in the ecological balance of supragingival biofilms, inhibition of caries, and also report its promising clinical applications in dentistry. The major points are the following: 1. the significance of arginine and its associated mechanism of action. 2. Potential of arginine to promote remineralization and decrease dentinal hypersensitivity. 3. To Provide oral health professionals with recommendations for using arginine in clinical practice.

KEYWORD : Dentistry, Arginine, Dental Caries, Biofilms.

1. INTRODUCTION

L-Arginine, also known as L-arg, belongs to the class of organic compounds known as l-alpha-amino acids. It is a glutamine family amino acid, a proteinogenic amino acid specifically. These are alpha-amino acids that have the L-configuration of the alpha-carbon atom. L-Arginine has been observed in most human tissues and has also been detected in most biofluids, including cerebrospinal fluid, feces, urine, and saliva. Within the cell, L-arginine is primarily located in the cytoplasm, mitochondria, and myelin sheath. L-Arginine exists in all eukaryotes, ranging from yeast to humans. It has a role as a nutraceutical, a biomarker, a micronutrient, an Escherichia coli metabolite, and a mouse

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metabolite. L-Arginine is a drug used for nutritional supplementation, as well as for treating dietary shortage or imbalance. It is a conjugate base of an L-arginine(1+), a conjugate acid of an L-arginine, and an enantiomer of a D-arginine[1].

Ernst Schulze, a German chemist was the first to isolate arginine(Arg) from the yellow lupin seedlings in 1886, profoundly used as a prebiotic biofilm modifier. Arginine is metabolized by certain oral bacteria present in supragingival biofilm, which produces citrulline, ornithine, CO2, adenosine triphosphate(ATP), and ammonia by ADS pathway, resulting in a rise of both cytoplasmic and environmental pH. Thus, helping the oral bacteria against the acids, ATP synthesis, increase in ΔpH to a relatively neutral environment favoring the ADS positive bacteria to compete against the caries pathogens[2]. This ADS activity contributes to a bioenergetic advantage balancing the pH homeostasis, microbial ecology, and pathogenicity. The group of oral bacteria that are known to express the ADS mainly include *Streptococcus sanguinis*, *Streptococcus gordonii*, *Streptococcus parasanguis*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus rattus*, certain *Lactobacillus* species, and a few spirochetes [2]. However, some acid-producing bacteria that are associated with caries also possess the ADS, including species of *Actinomyces* and *Bifidobacterium/Scardovia* [3].

2. ARGININE AND STUDIES

Arginine has been proven as a new compound in combination with fluoride and insoluble calcium compounds as management for dental caries. According to Kleinberg's studies, glucose and ammonia as a combination together contribute to plaque pH by acid and base formation, counteracting the caries metabolism process which follows the same pattern as Stephan curve[4]. These studies evaluated the pH response to substrates like urea and glucose, that aid in measuring the dynamics of acid-base metabolism of plaque biofilm in real-time as a critical pH rise factor[5,6]. Kleinberg conducted various in vitro and in vivo studies on the effects of glucose and arginine on various oral acidogenic bacteria and established a pivotal role and characteristic behavior of arginolytic bacteria and non-arginolyticbacteria[7,8].

These studies concluded that no single bacteria have any effect on plaque pH profile, whereas a combination of bacterias due to their integrated metabolic pathways have a profound effect on different levels of caries activity. Thus, Kleinberg quoted" that a deficiency in base formation can be equally important in caries development as excessive acid formation from fermentable carbohydrates".

A stimulated salivary secretion leads to a rise of pH as high as 8.3. When the pH is above neutrality, there is a release of several salivary components resulting in the formation of a complex structure of glycoprotein and calcium phosphate "(salivary precipitin- termed by Kleinberg)" which gets readily incorporated into the dental plaque. The calcium phosphate present in the salivary precipitin is 8 to 10 times more soluble in comparison with tooth mineral. Thus, serving as a sacrificial mineral, before the dissolution of the tooth mineral and helps in the remineralization of decalcified tooth tissue. According to Kleinberg's studies the salivary precipitin calcium phosphate levels are elevated in non-cariogenic when compared to cariogenic plaque. Hence, it is more effective in buffering and remineralization process. These inputs or findings help us understand the bacterial metabolism and natural defenses against dental caries along with giving us the framework in redesigning the metabolism. Besides, the Kleinberg design acted as a therapeutic base representing the saliva model will help us to change the biofilm-tooth interface and environmental condition from cariogenic to non-cariogenic thereby enhancing the ability to mineralize. The combination of arginine,

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insoluble calcium and one or more cariostatic anion is formulated by Kleinberg, which would form the plaque biofilm by the formation of the base, favoring the presence of arginolytic bacteria over non-arginolytic bacteria. Thus leading to a decrease in cariogenic biofilm flora. Secondly, the dissolution of tooth enamel is suppressed by mass action and reduction in the release of calcium by insoluble calcium compounds. During acid solubilization, calcium is released from the tooth mineralized structure, before the phosphate. Thus, the use of calcium is advocated over phosphate as a suppressant since calcium helps to counteract the second stage of Miller's caries process. The anions provide the buffering capacity that enhances the base formation and thereby neutralizes the arginine activity. The cariostatic anion plays a role as a supplement to the anti-carious activity of calcium and arginine. Kleinberg's composition together combats Miller's process[9].

3. ARGININE concerning CARIES

Dental caries is a multifactorial disease, exhibiting a complex etiology with the production of acids from dietary sugars and carbohydrates, at the interface of susceptible tooth surface and dental plaque[10,11,12]. Exposure of root surface and gingival recession acts as a supplementary or secondary factor for the cariogenic process[13]. Dental plaque is a highly diverse and complex biofilm that is structured and spatially organized, consisting of a metabolically integrated community of bacteria that interact and communicate through gene transfer and secretion of signaling molecules[13,20]. As a whole, specific species in the community are codependent, thereby, increasing the metabolic efficiency, stress resistance, and enhanced virulence in comparison with planktonic microbes[14,15]. A notable change in environment can trigger changes from healthy to a pathogenic plaque biofilm predisposing a site for initiation of a carious process[16]. Many of the bacterial species exhibit ADS pathway releasing ammonia from the arginine to neutralize plaque acids and adapt a new survival mechanism[40,12]. This averts the healthy biofilm from transforming into a cariogenic one[11,12]. To reduce the caries risk more work has been emphasized on remodeling the tooth structure by reducing its susceptibility to caries attack in comparison with the plaque biofilm model[17]. Hence, the probable courses to reduce caries attack by focusing the plaque biofilm include:

1. Reducing total biofilm mass
2. By inhibiting or reducing the bacterial acid production
3. Promoting the microbial hemostasis and providing an environmental balance favoring healthy organisms within the plaque.

Major developments have been made since the establishment of Kleinberg's early work on molecular genetics and ammonia to its physiological effect on caries and health[2,18]. Loss of urease activity, by loss of alkali generating potential in dental plaque, has a positive effect on dental caries[19,20]. Clinical studies have established that ammonia produced by the ADS pathway from arginine helps in reducing caries externally present in saliva. Clinical studies have shown that external supplements of arginine have a profound impact on both non-caries and active caries individuals through ADS activity[21].

Fluoride has great benefits on dental tissue and in combination with the anti-cariogenic agent can be used to reduce or prevent the caries process at an early stage by targeting the residual plaque biofilm[22]. Clinical trials have shown that arginine bio carbonate can be used as an alternative to fluoride toothpaste. The study inferred that the continuous use of this toothpaste for 2 years was as effective as 1100 ppm fluoride toothpaste in reducing cavity formation. The use of arginine containing mint, used for 1 year significantly reduced the formation of cavities than the placebo mint[23]. Arginine along with insoluble calcium

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compounds has a synergistic action potential for caries prevention. Thus along with the benefits of fluoride, arginine can be tested as a potential to tooth dentifrice. Hence, a new and novel dentifrice has been developed containing 1.5 % arginine, sodium monofluorophosphate, insoluble calcium base, clinically validated[17]. 2 years clinical trial of two dentifrices containing 1.5 % arginine, 1450 ppm of fluoride in calcium base with one containing dicalcium phosphate and other containing calcium carbonate was more efficacious than the dentifrice containing only 1450 ppm of fluoride[3].

4. ARGININE WITH RESPECT TO HYPERSENSITIVITY

Dentin hypersensitivity is one of the most common diseases among dental patients and is characterized by short, sharp pain arising from exposed dentin in response to stimuli, typically thermal, evaporative, tactile, osmotic, or chemical, and which cannot be ascribed to any other dental defect or disease, making it difficult and challenging for its diagnosis by the dental professional[24,25]. During the stage of tooth development, dentin is formed by odontoblasts containing thousands of tubules running perpendicular to the pulp chamber thereby differentiating itself from other mineralized tissue of the tooth. During dentin synthesis, the odontoblasts migrate away from the dentin enamel junction and dentinal tubules are formed. The dentinal tubule is composed of odontoblastic processes and dentinal fluid[26]. The dentin is hypersensitive due to exposed dentinal tubules, patent or connected to the pulp, making it a complex and multifactorial process[24,27]. Gingival recession due to abrasion or periodontal disease and acid erosion are the primary factors in exposing dentinal tubules. The treatment plan of dental hypersensitivity is based either on occluding dentinal tubules or by interference with nerve impulse transmission[27,28]. Many occluding agents like Fluoride varnish (22,500 ppm fluoride) and prescription level fluoride toothpaste and gels (5000 ppm fluoride [29,30,31] physically block the exposed dentinal tubules preventing the movement of dentinal fluid in the tubules, triggered from the external stimuli, eventually blocking the pain impulse[29,30,31]. Dentifrices like potassium nitrate have desensitizing effect on the nerve by causing depolarization of the nerve conduction making it less susceptible to stimuli thereby reducing the pain sensation. To derive the desired result, many novel products have been clinically tested when compared to traditional methods for better, longer, and effective treatment. The SEM studies have shown the use of arginine calcium carbonate dentifrice could completely occlude the dentinal tubules up to a depth of 2µm[27,32]. To deliver effective management of dentinal hypersensitivity along with arginine-based dentifrice, other factors like plaque control modification in diet, emphasis on increased salivary flow, buffering capacity, etc. would increase the pH of saliva and therefore show a long-lasting effect.

5. ARGININE WITH RESPECT TO RESTORATIVE MATERIAL

Glass ionomer cement (GIC) is widely used as a restorative material in dentistry. Its application in geriatric and pediatric is well documented and it is used as an atraumatic restorative cement in the community-based oral health program. It is the only cement that can release fluoride and exhibits cariostatic properties[33]. Secondary caries continues to be the prime concern of GIC restoration failure, despite the bioavailability of fluoride which tends to enhance remineralization as it exhibits a finite effect in biofilm control[34]. As fluoride release from GIC does not impede the growth of cariogenic bacteria, the disintegration of bacterial biofilm surrounding the margins of restoration is not optimum[35,36] leading to microleakage and subsequent secondary caries development. The biocompatibility and the chemical adhesive property of GIC lead to its extensive application in the clinical scenario thereby becoming important to project this material with biofilm modifying or inhibiting agents. With the incorporation of 4%arginine, no alteration was seen in the elemental composition of GIC. Hence, an unfeigned change is seen in the surface roughness as well as

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mechanical properties. Since 4% arginine serves as a filler, substituting silicon, aluminum ions, no deleterious effect is observed on the surface roughness, nanohardness, and biaxial flexural strength. The caries preventive potential of GIC restoration is seen to increase when arginine with an optimum concentration(4% wt.) was incorporated. This can lead to the replacement of GIC with arginine complemented GIC in all the cases then treated with restoration alone. For e.g.as a pit and fissure sealant application, atraumatic restorative treatment, etc. However, to implement this dental material for clinical use, a further crystallographic investigation needs to be carried out to confirm that the arginine enriched GIC proves to be a compatible material[37].

6. ARGININE WITH RESPECT TO ADHESIVE CEMENT

The failure rate of dental composite restoration due to secondary caries continues to be a chief concern[38]. Wherein, the replacement of the failed restoration contributes up to 75% of operative work[39]. The crevice production seen between the interface of tooth and adhesive layer arises due to polymerization shrinkage and improper composite layering technique[40,41]. According to recently quoted studies, the incorporation of 7% arginine into an empirical dental formulation showed no change in mechanical and physical properties. However, the release of arginine at a specific rate and concentration from the adhesive exhibited antibacterial effects in cariogenic conditions like low pH and high sugar availability. Thereby making 7% arginine benefitting to provide resistance against complex flexural stresses upon intraoral loading[42]. In a current study, arginine has been integrated with a two-step etch and rinse adhesive system presuming that it would provide a prebiotic-based buffering capacity for the prevention of secondary caries[43]. The composition of primer and adhesive was projected to be dimethacrylate and methacrylate monomers, ethanol, photo-initiators along with arginine at a weight concentration of 7%, 5%, and 10%. Hence, incorporation of 7% arginine, in adhesives demonstrated salient antibacterial effects with no alteration of mechanical properties of the adhesive[42].

7. ARGININE WITH RESPECT TO PREBIOTICS, PROBIOTICS AND ORAL CARE FORMULATION

The recent research strategies are being directed towards disintegrating the physical and metabolic activities of the biofilm keeping prevention of dysbiosis and the focus on ecological approaches intact with the prime objective to combat caries. Antimicrobial strategies or enhancing the growth of health-promoting bacteria is the main factor in such interventions which can be holistically summarized as a biotic modality of caries prevention that assimilates the use of probiotics and prebiotics. Arginine acts as an oral prebiotic, facilitates the growth of alkalogenic health-promoting bacteria like *Streptococcus sanguinis, Streptococcus parasanguinis,* and *Streptococcus gordonii*, while inhibiting the cariogenic bacteria like *Streptococcus Mutans* simultaneously. However, the disadvantage of the long-standing use of arginine is plaque alkalization, which promotes over growth of oral anaerobes such as *Porphyromonasgingivalis*[44].

According to Roberfroid, prebiotics is fermented food ingredients that can change the activity of resident microflora consequently benefitting the host health and well-being [45]. Roberfroid et al in 2010 quoted the consumption of certain dietary elements that can selectively modulate the native composition of the gut microbiota [46]. In the field of medicine, arginine has been extensively researched to avail it as an aid to improve the symptom of cardiovascular disease[47].

In contrast to prebiotics, probiotics are viable microbes, when implemented in optimal doses, can bestow health benefits. However, it remains to be the center of controversies as it is unable to withstand the constant debate on its benefits versus the adverse effects. The mechanism of action of probiotics is a conglomeration of local and systemic effects that are

inclusive of immune modulation, adhesion, co-aggregation, growth inhibition of microbes, and product of any acids with the predominant goal of replacing the pathogens or displacing them. The basis of probiotic administration depends on specific bacterial strains or combinations of strains and the stage of a disease process in which the probiotic is administered. Extensive research has been carried out on *Lactobacillus rhamnosus* GG as a probiotic exhibiting profound health benefits and showcasing antagonistic properties against cariogenic bacteria. However, the potential of this towards microbes in the oral environment is fleeting[48,49]. Currently, the administration of pre and probiotics together has enormous potential to give results against oral pathogen for optimum management of dental caries[50,51].

Though the inhibitory capacity of *Lactobacillus rhamnosus* GG is determined, L-arginine shows to disintegrate human oral biofilm detrimenting the adhesive properties of S.Mutans[52,53]. It has been shown that *Lactobacillus rhamnosus* GG has a role in coaggregation[54] of S. mutans, prevents the adherence of S. Mutans, exhibits the bacterial effect on S. Mutans, reduces insoluble extracellular polysaccharides, and diminishes the salivary count of S.Mutans[55]. Thus, the delivery of L-arg molecules towards ecologically-based caries preventive treatment is done through two pathways. 1st pathway: Prebiotic effect on oral arginolytic commensals like *S. sanguinis* and *S. gordonii* wherein the arginine augments the growth of arginolytic bacteria and subsequently affects the ecology of oral biofilm[56,57]. 2nd pathway: *Lactobacillus rhamnosus* GG utilizes L-arginine to create a balanced environment conducive to its development. The probiotic pathway additionally supplements the availability of *Lactobacillus rhamnosus* GG in the oral cavity facilitating sustenance[58,17]. This probiotic bacteriotherapy enhances the resistance towards pathogenic colonization and shows immunomodulation potential. The synergistic mechanism of this symbiotic therapy will bait the formation of biofilm. Quoting Bejile MN et al, "L-arginine enhance the growth of *Lactobacillus rhamnosus* GG". The study showed the combination of 2 % L-arginine and *Lactobacillus rhamnosus* GG has a synergistic effect by inhibiting the growth of S.Mutans and has a noteworthy use as an anticaries regimen[59].

According to Parwani and Parwani studies, supplementation of arginine has a positive effect in supragingival biofilm and the nitrous oxide that is synthesized during arginine metabolism plays a role in the pathogenic process of periodontitis[60]. For further validation, L-arginine as dietary supplementation, long term clinical trials are forecasted[56].

8. CONCLUSION

Dental caries is a predominant global oral health disease. A constant evolution in the prevention/ treatment of dental caries has been witnessed[61]. However, this dual approach of combining agents and targeting dental plaque will consequently control the initiation and inhibition in the formation of biofilm which can serve as a game-changer. However, protective bases of oral alkali production have to find their way into commercial use with the prime vision of being accessible, cost-effective, biocompatible and exhibit minimal side effects[22].

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