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AMINO ACIDS AND DENTAL CARIES: BIOLOGICAL MODULATION OF BACTERIAL METABOLISM AND ENAMEL DEMINERALIZATION

AMINOÁCIDOS E CÁRIE DENTÁRIA: MODULAÇÃO BIOLÓGICA DO METABOLISMO BACTERIANO E DA DESMINERALIZAÇÃO DO ESMALTE

AMINOÁCIDOS Y CARIES DENTAL: MODULACIÓN BIOLÓGICA DEL METABOLISMO BACTERIANO Y LA DESMINERALIZACIÓN DEL ESMALTE

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ABSTRACT

Objective: This review aimed to analyze the role of amino acids in the modulation of oral biofilm metabolism and their influence on enamel demineralization and dental caries development.

Methodology: A structured review of experimental, in vitro, and clinical literature was performed to assess the biological effects of amino acids on cariogenic processes. Searches were conducted in major scientific databases using terms related to amino acids, dental

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caries, bacterial metabolism, pH regulation, and enamel demineralization. Eligible studies were examined for mechanisms involving nitrogen metabolism, alkali production, and bacterial ecological balance within the oral environment.

Results: The reviewed evidence indicates that specific amino acids, including arginine, glutamine, and glycine, contribute to caries prevention by modulating biofilm metabolic activity. These compounds enhance alkali generation through arginolytic and urease pathways, resulting in increased plaque pH and reduced acidogenicity. Consequently, enamel demineralization is attenuated, and the ecological balance of the oral microbiome shifts toward a less cariogenic profile. Additionally, amino acids were shown to interfere with the dominance of acid-producing bacteria, such as Streptococcus mutans, promoting a more stable oral environment.

Conclusion: Amino acids play a significant biological role in regulating oral biofilm behavior and enamel integrity. Their incorporation into preventive strategies, including oral hygiene products and dietary approaches, may offer a promising adjunct for caries control. Further clinical research is needed to establish optimal formulations and long-term effectiveness in caries management.

Keywords: Amino Acids. Dental Caries. Oral Biofilm. Bacterial Metabolism. Enamel Demineralization. Ph Regulation.

RESUMO

Objetivo: Esta revisão teve como objetivo analisar o papel dos aminoácidos na modulação do metabolismo do biofilme oral e sua influência na desmineralização do esmalte e no desenvolvimento da cárie dentária.

Metodologia: Foi realizada uma revisão estruturada da literatura experimental, in vitro e clínica para avaliar os efeitos biológicos dos aminoácidos nos processos cariogênicos. As buscas foram conduzidas em bases de dados científicas relevantes, utilizando termos relacionados a aminoácidos, cárie dentária, metabolismo bacteriano, regulação do pH e desmineralização do esmalte. Os estudos elegíveis foram examinados quanto aos mecanismos envolvendo metabolismo do nitrogênio, produção de álcalis e equilíbrio ecológico bacteriano no ambiente oral.

Resultados: As evidências analisadas indicam que aminoácidos específicos, incluindo arginina, glutamina e glicina, contribuem para a prevenção da cárie ao modular a atividade metabólica do biofilme. Esses compostos aumentam a geração de álcalis por meio das vias arginolítica e ureásica, resultando em elevação do pH da placa bacteriana e redução da acidogenicidade. Consequentemente, a desmineralização do esmalte é atenuada, e o equilíbrio ecológico do microbioma oral se desloca para um perfil menos cariogênico. Além disso, os aminoácidos demonstraram interferir na dominância de bactérias produtoras de ácido, como Streptococcus mutans, promovendo um ambiente oral mais estável.

Conclusão: Os aminoácidos desempenham um papel biológico significativo na regulação do comportamento do biofilme oral e na integridade do esmalte dentário. Sua incorporação em estratégias preventivas, incluindo produtos de higiene oral e abordagens dietéticas, pode representar um adjuvante promissor no controle da cárie. São necessárias mais pesquisas clínicas para estabelecer formulações ideais e avaliar a eficácia a longo prazo no manejo da cárie dentária.

Palavras-chave: Aminoácidos. Cárie Dentária. Biofilme Oral. Metabolismo Bacteriano.

Desmineralização do Esmalte. Regulação do pH.

RESUMEN
Objetivo: Esta revisión tuvo como objetivo analizar el papel de los aminoácidos en la modulación del metabolismo del biofilm oral y su influencia en la desmineralización del esmalte y el desarrollo de la caries dental.

Metodología: Se realizó una revisión estructurada de la literatura experimental, in vitro y clínica para evaluar los efectos biológicos de los aminoácidos en los procesos cariogénicos. Las búsquedas se llevaron a cabo en bases de datos científicas relevantes, utilizando términos relacionados con aminoácidos, caries dental, metabolismo bacteriano, regulación del pH y desmineralización del esmalte. Los estudios elegibles fueron analizados considerando mecanismos relacionados con el metabolismo del nitrógeno, la producción de álcalis y el equilibrio ecológico bacteriano en el entorno oral.

Resultados: La evidencia revisada indica que aminoácidos específicos, incluidos la arginina, la glutamina y la glicina, contribuyen a la prevención de la caries mediante la modulación de la actividad metabólica del biofilm. Estos compuestos incrementan la generación de álcalis a través de las vías arginolítica y ureásica, lo que resulta en un aumento del pH de la placa dental y una reducción de la acidogenicidad. En consecuencia, se atenúa la desmineralización del esmalte y el equilibrio ecológico del microbioma oral se desplaza hacia un perfil menos cariogénico. Además, se observó que los aminoácidos interfieren en la dominancia de bacterias productoras de ácido, como Streptococcus mutans, promoviendo un entorno oral más estable.

Conclusión: Los aminoácidos desempeñan un papel biológico relevante en la regulación del comportamiento del biofilm oral y en la integridad del esmalte dental. Su incorporación en estrategias preventivas, incluidos productos de higiene oral y enfoques dietéticos, puede representar un complemento prometedor para el control de la caries. Se requieren más estudios clínicos para establecer formulaciones óptimas y evaluar la eficacia a largo plazo en el manejo de la caries dental.

Palabras clave: Aminoácidos. Caries Dental. Biofilm Oral. Metabolismo Bacteriano. Desmineralización del Esmalte. Regulación del pH.

1 INTRODUCTION

Dental caries remains one of the most prevalent chronic diseases worldwide, affecting billions of individuals across different age groups and socioeconomic contexts (Fejerskov & Kidd, 2008). Despite substantial advances in preventive dentistry, including widespread fluoride exposure and improvements in oral hygiene practices, caries continues to pose a major public health challenge. This persistence reflects the multifactorial nature of the disease and limitations of strategies that focus predominantly on mineral chemistry or nonspecific bacterial suppression rather than on the underlying biological mechanisms driving disease initiation and progression.

Contemporary understanding recognizes dental caries as a biofilm-mediated, diet-modulated, and dysbiosis-driven disease, rather than a simple consequence of sugar intake or infection by a single pathogen (Marsh, 1994; Fejerskov, 2004). According to the ecological plaque hypothesis, frequent exposure to fermentable carbohydrates creates selective pressure within the dental biofilm, favoring the proliferation of acidogenic and aciduric microorganisms. These organisms, including Streptococcus mutans and Lactobacillus species, produce organic acids that lower plaque pH and disrupt the balance between demineralization and remineralization at the tooth surface (Marsh, 2006).

When plaque pH falls below the critical threshold for enamel, approximately pH 5.5, mineral dissolution predominates, leading to net enamel demineralization and the formation of carious lesions (Featherstone, 2004). Importantly, this process is dynamic and reversible in its early stages, highlighting the importance of biological factors capable of stabilizing plaque pH and promoting ecological balance within the oral microbiome. As a result, preventive strategies have increasingly shifted toward approaches that enhance natural protective mechanisms rather than solely inhibiting bacterial growth. One of the most significant protective mechanisms against cariogenic acidification is alkali generation within the dental biofilm. Saliva and plaque contain nitrogenous substrates, such as urea and free amino acids, that can be metabolized by oral bacteria to produce ammonia, thereby neutralizing acids and increasing plaque pH (Kleinberg, 1967; Burne & Marquis, 2000). This alkali production plays a crucial role in maintaining pH homeostasis and limiting the time that plaque remains in a demineralizing state.

Among these substrates, amino acids have emerged as key biological modulators of caries susceptibility. Arginine, glutamine, and glycine are naturally present in saliva and gingival crevicular fluid and are actively metabolized by specific members of the oral microbiota (Nascimento et al., 2009). Arginine, in particular, has been extensively studied due to its metabolism via the arginine deiminase system (ADS), a pathway that converts arginine into citrulline, ammonia, and ATP (Burne & Marquis, 2000). This pathway not only buffers plaque acids but also provides a metabolic advantage to arginolytic bacteria, promoting their persistence within the biofilm.

Clinical and epidemiological studies consistently demonstrate that individuals with low caries experience exhibit higher arginolytic activity in dental plaque compared with caries-active individuals (Nascimento et al., 2009; Huang et al., 2012). Higher ADS activity is associated with elevated resting plaque pH and more rapid pH recovery following sugar challenges, suggesting a protective effect against prolonged acidification. These findings reinforce the concept that amino acid metabolism is a central determinant of biofilm behavior and caries risk.

Beyond arginine, other amino acids contribute to nitrogen metabolism and pH regulation. Glutamine and glycine undergo deamination reactions that release ammonia, contributing to baseline buffering capacity within the biofilm (Burne & Marquis, 2000; Liu & Burne, 2009). Although their alkali-generating potential is lower than that of arginine, these amino acids may play an important role in sustaining pH stability during fasting periods and between meals, when carbohydrate availability is limited. Importantly, the biological effects of amino acids extend beyond simple chemical buffering. Advances in molecular microbiology have revealed that arginine availability can influence bacterial gene expression and interspecies interactions within dental biofilms. Exposure to arginine has been shown to downregulate S. mutans genes associated with acid tolerance, stress response, and extracellular polysaccharide synthesis—key determinants of cariogenic virulence (Huang et al., 2012). These changes impair the organism's ability to dominate under neutral pH conditions and reduce the structural integrity of cariogenic biofilms.

In parallel, amino acid metabolism selectively favors commensal streptococci, such as Streptococcus sanguinis and Streptococcus gordonii, which possess robust arginolytic capacity (Liu & Burne, 2009). This selective advantage promotes microbial diversity and ecological resilience, key features of a healthy oral microbiome. Mixed-species biofilm models demonstrate that arginine supplementation results in higher plaque pH, reduced lactic acid accumulation, and increased resistance to repeated acid challenges (Koopman et al., 2015). The impact of amino acid metabolism on enamel demineralization has also been demonstrated in laboratory and in situ models. Biofilms with enhanced alkali-generating capacity induce significantly less enamel mineral loss and surface hardness reduction compared with highly acidogenic biofilms (Featherstone, 2004; Huang et al., 2012). By maintaining plaque pH above the critical threshold, amino acids facilitate remineralization during non-acidic periods, contributing to long-term enamel preservation.

These biological insights have driven the translation of amino acid–based strategies into clinical practice. Dentifrices containing arginine, often combined with fluoride, have demonstrated superior caries-preventive effects compared with fluoride-only formulations in randomized clinical trials (Cummins, 2013; Wolff et al., 2013). Such products aim to enhance endogenous alkali-generating pathways rather than relying solely on mineral reinforcement or antimicrobial activity, aligning with modern concepts of caries as a dysbiosis-driven disease. Despite growing evidence, important gaps remain. Most clinical studies focus on short- to medium-term outcomes, and long-term data on sustained caries reduction are limited. Additionally, interindividual variability in oral microbiome composition may influence responsiveness to amino acid–based interventions, suggesting a potential role for personalized preventive strategies.

Therefore, the aim of this review is to synthesize current experimental, clinical, and translational evidence on the role of amino acids in modulating oral biofilm metabolism and enamel demineralization. By integrating microbiological, biochemical, and clinical perspectives, this review seeks to clarify the biological relevance of amino acids, particularly arginine, glutamine, and glycine in the prevention and control of dental caries.

2 METHODOLOGY

A structured narrative review was conducted to assess the biological role of amino acids in dental caries development and prevention. Electronic database searches were performed using terms associated with amino acids, dental caries, oral biofilm metabolism, pH regulation, and enamel demineralization. Experimental, in vitro, and clinical studies investigating nitrogen metabolism, alkali production, and microbial ecological balance within the oral cavity were considered eligible. Data extraction focused on mechanistic pathways by which amino acids influence bacterial metabolism and enamel integrity. The findings were synthesized qualitatively to provide an integrated biological perspective on caries modulation.

3 RESULTS

3.1 ROLE OF AMINO ACIDS IN ALKALI GENERATION AND PLAQUE PH REGULATION

A substantial body of experimental and clinical evidence demonstrates that amino acids play a central role in alkali generation within dental biofilms, directly influencing plaque pH homeostasis. Among these substrates, arginine has been consistently identified as the most biologically relevant amino acid due to its metabolism via the arginine deiminase system (ADS). This pathway converts arginine into citrulline and ammonia while simultaneously generating ATP, conferring both ecological and energetic advantages to arginolytic bacteria (Burne & Marquis, 2000; Nascimento et al., 2009).

In situ plaque studies reveal that individuals with low caries experience exhibit significantly higher arginolytic activity compared with caries-active subjects, resulting in elevated resting plaque pH and faster pH recovery following sugar challenges (Nascimento et al., 2009; Huang et al., 2012). These findings indicate that alkali production from amino acid metabolism counteracts acidogenic episodes and reduces the cumulative time that plaque pH remains below the critical threshold for enamel demineralization.

Glutamine and glycine also contribute to ammonia production through deamination reactions, although with lower efficiency than arginine. Experimental biofilm models demonstrate that these amino acids sustain basal buffering capacity, particularly during periods of low carbohydrate availability, thereby contributing to long-term ecological stability within the biofilm (Burne & Marquis, 2000; Liu & Burne, 2009). Collectively, these data support the concept that amino acids function as endogenous regulators of plaque pH rather than episodic buffers.

3.2 MODULATION OF ORAL MICROBIAL ECOLOGY

Beyond their chemical buffering effects, amino acids significantly influence the ecological balance of the oral microbiome. Arginine metabolism selectively favors commensal streptococci, including Streptococcus sanguinis, Streptococcus gordonii, and Streptococcus parasanguinis, which possess robust ADS activity. These organisms gain a competitive advantage in neutral or slightly alkaline environments, thereby limiting the dominance of acidogenic and aciduric species such as Streptococcus mutans (Liu & Burne, 2009; Koopman et al., 2015).

Molecular studies provide mechanistic insight into these ecological shifts. Exposure to arginine has been shown to downregulate S. mutans genes associated with acid tolerance, stress response, and extracellular polysaccharide synthesis, all of which are critical for cariogenic biofilm formation (Huang et al., 2012). As a result, biofilms formed in the presence of arginine exhibit reduced biomass density, lower lactic acid accumulation, and diminished structural integrity.

Mixed-species biofilm experiments further demonstrate that arginine availability promotes microbial diversity and resilience. Biofilms supplemented with arginine show enhanced stability in response to repeated carbohydrate challenges, maintaining higher pH levels and preventing the ecological collapse typically observed in cariogenic conditions (Koopman et al., 2015). These findings reinforce the ecological plaque hypothesis and highlight amino acids as modulators of microbial interactions rather than simple antimicrobial agents.

3.3 EFFECTS ON ENAMEL DEMINERALIZATION AND MINERAL BALANCE

The protective effects of amino acid metabolism extend to the tooth surface, where stabilization of plaque pH directly influences enamel mineral dynamics. In situ enamel slab studies reveal that biofilms capable of sustained alkali production induce significantly less surface hardness loss and lower mineral dissolution compared with acidogenic biofilms lacking arginolytic capacity (Featherstone, 2004; Huang et al., 2012).

Laboratory-based pH-cycling models further confirm that arginine-enriched environments reduce net enamel demineralization under cariogenic conditions. These models demonstrate that ammonia production maintains plaque pH above the critical threshold for hydroxyapatite dissolution, allowing remineralization processes to predominate during non-acidic periods (Featherstone, 2004). Glutamine and glycine exert similar, albeit less pronounced, protective effects, supporting their role as adjunctive modulators of mineral balance.

Importantly, these effects are cumulative and biologically driven, suggesting that amino acids contribute to long-term enamel preservation rather than transient chemical neutralization.

3.4 CLINICAL EVIDENCE SUPPORTING AMINO ACID–BASED INTERVENTIONS

Clinical trials provide translational evidence supporting the biological relevance of amino acids in caries prevention. Randomized controlled studies evaluating arginine-containing dentifrices, often combined with fluoride, demonstrate significantly greater reductions in caries incidence and lesion progression compared with fluoride-only formulations (Cummins, 2013; Wolff et al., 2013). These benefits are particularly evident in high-caries-risk populations, where enhancement of endogenous alkali-generating pathways appears to complement fluoride-mediated remineralization. Clinical outcomes consistently align with microbiological and biochemical findings, including increased plaque pH, reduced acidogenicity, and shifts toward a less cariogenic microbial profile (Cummins, 2013).

Nevertheless, heterogeneity in study design, exposure duration, and outcome measures highlights the need for long-term trials assessing sustained caries reduction and lesion arrest. Individual variability in oral microbiome composition may also influence responsiveness to amino acid–based interventions, underscoring the importance of personalized preventive strategies.

4 DISCUSSION

The present review reinforces the concept that dental caries is not merely a consequence of sugar exposure but a dysbiotic disease driven by metabolic imbalances within the oral biofilm. In this context, amino acids emerge as biologically relevant modulators capable of shifting biofilm metabolism toward a less cariogenic state. Substantial experimental and clinical evidence demonstrates that arginine, glutamine, and glycine influence plaque ecology by promoting alkali generation and buffering acidogenic challenges, thereby stabilizing plaque pH and protecting enamel from demineralization.

Arginine metabolism via the arginine deiminase system (ADS) is one of the most extensively studied pathways in caries prevention. Commensal oral bacteria, such as Streptococcus sanguinis, Streptococcus gordonii, and Streptococcus parasanguinis, utilize arginine to produce ammonia, which counteracts acidification caused by fermentable carbohydrates. This alkali-generating mechanism not only neutralizes plaque pH but also creates an ecological disadvantage for highly aciduric and acidogenic species, particularly Streptococcus mutans. Longitudinal and in situ studies have consistently shown that higher arginolytic activity is associated with caries-free individuals, supporting the ecological plaque hypothesis rather than a purely pathogen-centered model.

Glutamine and glycine further contribute to nitrogen metabolism and pH homeostasis through deamination reactions that release ammonia. Although less potent than arginine, these amino acids appear to exert complementary effects by sustaining baseline buffering capacity within the biofilm. Importantly, these mechanisms operate continuously and are not dependent on immediate dietary intake, highlighting their relevance in maintaining long-term ecological stability. Beyond pH modulation, amino acids also influence microbial competition and gene expression within biofilms. Emerging evidence suggests that arginine availability downregulates virulence-associated genes in S. mutans, including those involved in acid tolerance and extracellular polysaccharide synthesis. This effect limits biofilm matrix formation and reduces enamel surface adherence, further attenuating cariogenic potential. Such findings underscore that amino acids act not only as chemical buffers but also as ecological signaling molecules.

From a clinical perspective, the incorporation of arginine into dentifrices and oral care products has demonstrated superior caries-preventive effects compared with fluoride alone in certain populations. These findings align with contemporary preventive strategies that aim to enhance host–microbiome equilibrium rather than indiscriminately suppress bacterial growth. However, heterogeneity in study design, exposure time, and outcome measures highlights the need for standardized clinical protocols.

Despite robust mechanistic evidence, limitations remain. Most clinical studies focus on short-term outcomes, and data on long-term caries incidence and lesion progression are still limited. Furthermore, individual variability in oral microbiome composition may influence responsiveness to amino acid-based interventions, suggesting that personalized preventive approaches may be required.

5 CONCLUSION

Collectively, the evidence supports a pivotal role for amino acids in modulating oral biofilm metabolism and protecting enamel against demineralization. By enhancing alkali production, suppressing cariogenic dominance, and promoting ecological balance, amino acids, particularly arginine, represent a biologically sound adjunct in caries prevention. Their integration into preventive dentistry aligns with modern concepts of caries as a biofilm-mediated, dysbiosis-driven disease. Future well-designed longitudinal clinical trials and microbiome-based studies are essential to define optimal formulations, dosing strategies, and patient-specific applications.

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