

The Mechanism and Application of Glutathione in the Prevention and Treatment of Dental Caries

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Abstract: Dental caries, as one of the three major chronic diseases worldwide, is closely associated with oxidative-antioxidative imbalance in the oral cavity. Glutathione (GSH), a crucial endogenous antioxidant in the oral environment, plays a dual role in caries development through scavenging reactive oxygen species (ROS), modulating immune microenvironment, and influencing cariogenic biofilm formation. This review systematically examines the molecular mechanisms of GSH and its complex relationship with dental caries, including the controversial correlation between salivary GSH levels and caries activity, as well as the role of GSH-related enzymes in caries progression. Furthermore, we discuss the mechanisms by which *Streptococcus mutans* enhances oxidative stress tolerance through GSH metabolism, and analyze the therapeutic potential of GSH in caries management, particularly its combined use with silver diamine fluoride (SDF) or silver nanoparticles (AgNPs) to reduce tooth discoloration while enhancing antibacterial efficacy. GSH-mediated regulation of oxidative stress, cariogenic virulence, and remineralization processes offers novel insights for caries prevention and treatment. Future multicenter clinical studies are warranted to elucidate the dynamic changes of GSH and develop precision anti-caries strategies based on oxidative stress modulation.

Keywords: Glutathione; Dental Caries; Oxidative Stress; Antioxidant; Oral Microbiota.

1. Introduction

Dental caries is one of the most prevalent chronic diseases globally and is listed by the World Health Organization as one of the three major diseases to focus on, alongside cancer and cardiovascular diseases. Its incidence increases significantly with age [1]. The occurrence and development of dental caries is a complex process involving multiple factors, with oxidative stress and the dynamic balance of antioxidant defense systems playing a key regulatory role in the disease process. Research by Yas et al. [2] confirmed that the levels of free radicals in the oral cavity are significantly elevated in the caries state, and excess reactive oxygen species (ROS) not only damage the function of local immune cells but also promote the colonization of cariogenic microorganisms on the tooth surface and accelerate biofilm formation, thus exacerbating caries progression. GSH, as the most important endogenous antioxidant in the human body, plays a central role in maintaining oral immune homeostasis and redox balance. Existing studies have shown that the antioxidant activity of GSH is significantly correlated with the pathogenicity of major cariogenic microorganisms and the development of dental caries [3, 4]. With the increasing clinical application of GSH-containing preparations, the potential impact of these drugs, whether taken orally or used topically, on the progression of dental caries needs to be further studied. This article aims to systematically analyze the latest research evidence and comprehensively elucidate the multidimensional mechanisms by which GSH regulates the occurrence and development of dental caries.

2. Molecular Characteristics and Antioxidant Mechanism of Glutathione

Glutathione is a tripeptide molecule composed of γ -

glutamyl-cysteinyl-glycine, with structural features that include an active thiol group (-SH) and a specific γ -amide bond [5]. Under physiological conditions, glutathione exists mainly in two forms: reduced (GSH, accounting for 95%-98%) and oxidized (GSSG), with the biological activity of GSH relying on its γ -glutamyl group and the free thiol group of cysteine residues. As a key antioxidant molecule, GSH exerts its cell-protective effects through the following mechanisms: (1) neutralizing free radicals; (2) inhibiting membrane lipid peroxidation; (3) chelating heavy metals and other exogenous toxic substances [6]. The antioxidant function of GSH is primarily mediated through the glutathione peroxidase-reductase system (GSH-Px-Rx). In this system, GSH-Px catalyzes the reduction of H₂O₂ to H₂O while protecting polyunsaturated fatty acids in the cell membrane from oxidative damage, thereby maintaining membrane structure stability. This system also continuously reduces the oxidized form (GSSG) back to active GSH, thereby maintaining the dynamic balance of the cell's antioxidant capacity. Clinical observations have shown that even if dialysis patients maintain normal antioxidant vitamin levels, their antioxidant capacity may still significantly decrease due to defects in the GSH and related enzyme systems [7]. In the oral environment, the redox balance mediated by GSH plays a dual regulatory role in maintaining local immune homeostasis and microbial ecological balance. On one hand, changes in GSH levels can affect immune cell function; on the other hand, its antioxidant state directly participates in regulating the virulence expression of cariogenic bacteria, and this complex interaction network ultimately affects the occurrence and development of dental caries.

3. Regulatory Role of Glutathione in the Caries Process

3.1. Saliva and the Balance of Oxidative Stress and Caries Susceptibility

Saliva, as an important defense barrier in the oral cavity, plays a key role in maintaining oral health through its buffering system and antioxidant defense mechanisms. Studies have shown that the antioxidant components in saliva maintain a precise dynamic balance with ROS [8]. Moderate levels of ROS can activate the immune function of macrophages [9], while excessive ROS led to oxidative damage. This balance directly influences the occurrence and development of caries [10]. Among the many antioxidant components in saliva, GSH is particularly notable for its special antioxidant properties. Existing studies confirm that oxidative stress markers, including GSH, not only serve as diagnostic indicators for caries, periodontitis, and other oral inflammatory diseases [3, 11-13], but their level changes are also significantly correlated with the progression of caries. Clinical data show that in caries patients, the expression levels of oxidative damage markers in saliva are significantly elevated and positively correlated with the severity of carious lesions [14]. These findings provide new research directions for monitoring caries progression through salivary biomarkers.

3.2. Controversial Association Between Salivary Glutathione Levels and Caries Activity

In patients with active caries, total salivary GSH levels may be compensatorily elevated due to oxidative stress, but the relationship with the severity of caries remains controversial [2]. Studies have shown that individuals with active caries have higher antioxidant levels, and the total glutathione concentration has a significant positive linear relationship with caries prevalence. Moreover, individuals with higher GSH levels in their saliva have higher levels of *Lactobacillus* (LB) and *Mutans Streptococci* (MS), and the levels of these bacteria are positively correlated with the DMFT index in children. On the other hand, environments rich in GSH and GSSH favor the growth and survival of cariogenic bacteria such as *Lactobacillus* and *Mutans Streptococci*, thereby exacerbating the progression of caries. Individuals with lower GSH levels are more likely to be spared from caries, and the increase in antioxidant levels may be an adaptive response to oxidative stress [3]. Yas et al. found a significant correlation between total salivary glutathione, salivary flow rate, and root caries severity in patients of different genders and ages, with a positive correlation to root caries severity. Additionally, patients with symptoms of reduced salivation had significantly higher total GSH levels than those with normal salivation [2]. The author believes that elevated GSH levels result from changes in microbial composition, which accelerate caries development. Wang Yu et al. also believe that the GSH system, as an important antioxidant mechanism, is closely related to the body's oxidative stress levels. In children with caries and nephrotic syndrome, the levels of salivary oxidative stress markers increase, and the content of antioxidants such as GSH increases as the number of carious lesions and the extent of decay worsen [15].

3.3. The Association of Glutathione Metabolic Enzyme Systems with Caries

Hendi et al. studied the levels of peroxidase, uric acid, catalase, glutathione peroxidase (GSH-Px, GPx), and superoxide dismutase (SOD) in caries and gender as variables. The results showed that the GSH-Px level in the caries-active group was higher than that in the non-caries group, with the difference being most significant for GSH-Px. The level of catalase was lower in females than in males, while SOD levels were higher, and GPx levels were less influenced by gender [26].

4. Glutathione and its Association with *Streptococcus mutans*

4.1. Glutathione-Dependent Stress Response of Cariogenic Microorganisms

Streptococcus mutans is one of the primary cariogenic bacteria. Its rapid acid metabolism, acid tolerance, and resistance to reactive electrophile species (RES) and cellular oxidative stress establish its ecological competitiveness in biofilms [27, 28]. Studies show that when the antioxidant level of *Streptococcus mutans* decreases, its virulence and biofilm competitiveness weaken [29]. Unlike other cariogenic bacteria, *Streptococcus mutans* lacks catalase, and therefore relies on other mechanisms to combat oxidative stress [30, 31]. These include synthesizing various reductases like superoxide dismutase (SOD) and NADH oxidase (Nox) to counter oxidative stress, and using bacterial metal regulatory proteins such as Dpr, Slo R, and Per R to regulate essential coenzyme factors like iron (Fe) and manganese (Mn) within the bacterial cell, thus inhibiting the Fenton reaction and converting harmful hydroxyl radicals to protect against oxidative stress [32]. It has also been discovered that the spx gene-produced transcription factor Spx plays an important regulatory role in *Streptococcus mutans*' oxidative stress response [33]. The *Streptococcus mutans* gor gene, gsh AB gene, and its ability to absorb exogenous glutathione are other important mechanisms involved in antioxidant stress through protein S-glutathionylation [34].

4.2. Glutathione Reductase System

Glutathione reductase is a key enzyme that recycles GSSH to GSH. A study by Wang Yu et al. [15] indicated that the glutathione-related enzyme system in children with nephrotic syndrome interferes with the metabolism of GSH, leading to changes in oxidative stress levels in the oral cavity. It was found that *Streptococcus mutans* with a defective glutathione reductase gor gene could grow under aerobic conditions, but stopped growing in the thiol oxidant diamide environment. In contrast, wild-type strains grew unaffected in diamide environments. Furthermore, the gor gene-deficient strain could recover growth when exogenous glutathione was added. The glutathione reductase activity level in the wild-type strains significantly increased after exposure to air. These results suggest that exogenous glutathione and glutathione reductase participate in the oxidative stress response of *Streptococcus mutans* in oxidative stress environments. Additionally, it was discovered that *Streptococcus mutans* can utilize glutathione to tolerate antibiotics such as gentamicin and vancomycin [35]. This indicates that *Streptococcus mutans* strains with high levels of glutathione and active glutathione reductase are more resistant to immune

system and antibiotic damage, enabling them to survive in higher oxidative stress environments, thus gaining an ecological advantage in the oral microbiome and exacerbating caries development.

4.3. Antioxidant Role of gshAB Bifunctional Enzyme

GSH is synthesized by glutamate-cysteine ligase (gshA) and glutathione synthetase (gshB). In *Streptococcus mutans*, the gshAB gene encodes a bifunctional enzyme that simultaneously possesses the functional domains of glutamate-cysteine ligase and glutathione synthetase. This enzyme plays an important role in oxidative stress and competition with hydrogen peroxide-producing bacteria. Studies have shown that although the lack of gshAB in *Streptococcus mutans* does not significantly affect its growth under aerobic conditions, the strain becomes more sensitive to H₂O₂. Additionally, due to the lack of the ability to combat peroxide produced by other bacteria, the gshAB-deficient strain exhibits reduced competitiveness against other bacteria like *Streptococcus sanguinis* [36].

4.4. Protein S-glutathionylation Modification

S-glutathionylation is an important post-translational modification (PTM) process in which glutathione is added to the cysteine thiol group of proteins to prevent excessive oxidation of protein cysteine residues under oxidative or nitrosative stress conditions. Li et al. conducted site-directed mutagenesis on thioredoxin-like protein (Tlp) and found that the glutathionylation of the Tlp Cys41 residue plays a critical role in protecting *Streptococcus mutans* from oxidative stress and competing with *Streptococcus sanguinis* and *Streptococcus gordonii*. They also demonstrated that the absence of S-glutathionylation reduces the cariogenicity of *Streptococcus mutans* [37].

5. Glutathione-Based Caries Treatment Strategies

Silver ions, known for their antibacterial properties and lack of resistance, have been widely used in medical and food industries [38]. However, their application is limited by their tendency to oxidize. GSH can effectively alleviate the exposure to silver ions and is used in silver ion coatings, referred to as the best supplement for silver [39]. Recent developments in nanoscience have also supported the use of silver and GSH, making it more efficient, safe, and precise.

5.1. Glutathione-Modified Silver Diamine Fluoride

Silver diamine fluoride (SDF) is an economically efficient caries preventive agent with significant application value in community-based oral disease prevention. However, its clinical promotion is significantly limited by the problem of tooth discoloration after treatment [40]. Recent studies have shown that adding 20% reduced GSH to SDF effectively improves enamel and dentin discoloration, and the combination does not affect the anti-caries efficacy of SDF [41]. Subsequent studies also found that the combined application of GSH and SDF did not increase the risk of microleakage after tooth restoration and did not change the bonding strength with dentin. It enhanced the bonding strength with glass ionomer cement, even outperforming the bonding strength of SDF or SDF-KI solutions alone [42-44].

It also reduced the toxic effects of SDF on pulp cells when used alone [45]. Additional studies have shown that GSH combined with SDF improves the anti-acid erosion effect of dentin and cementum, promotes remineralization of demineralized dentin, and enhances mechanical properties, with no significant difference from using SDF alone. Furthermore, the addition of GSH does not affect the binding of silver ions to hydroxyapatite and collagen fibers [46]. These findings provide an important theoretical basis for developing improved SDF formulations.

5.2. Glutathione-Functionalized Silver Nanoparticles for Antibacterial Systems

Silver nanoparticles (AgNPs), due to their antibacterial activity, have been proposed as alternatives to restrict bacterial biofilm formation. New glutathione-stabilized silver nanoparticles (GSH-AgNPs) have been shown to have strong antibacterial properties in food manufacturing. Studies by Zorraquín-Peña and Lu [47, 48] indicate that GSH-AgNPs significantly inhibit *Streptococcus mutans*, and at concentrations that inhibit *Streptococcus mutans*, the cytotoxic effect is not significant. Feng Jing et al., in their green synthesis of silver nanoparticles with the assistance of GSH, demonstrated its inhibitory activity against several cariogenic and periodontal pathogens, confirming the broad-spectrum antibacterial ability of GSH-AgNPs and their potential use in oral care [49].

Currently, various studies are being conducted on drugs using GSH as a stabilizer and adjuvant, some of which have already been applied in clinical settings, especially those with improved coloring or broad-spectrum antibacterial properties. More similar drugs will be put into use in the future, providing new solutions for the treatment of oral diseases [50].

6. Summary and Outlook

Research on the mechanisms of glutathione (GSH) and its therapeutic applications in dental caries is still in its preliminary stages. Existing evidence suggests that GSH is multidimensionally associated with caries development through regulating the oral oxidative-antioxidative balance, affecting the virulence of cariogenic bacteria (e.g., the expression of gshAB in *Streptococcus mutans*), and participating in the remineralization process. However, due to heterogeneity in research samples (such as age, overall health conditions), differences in detection methods, and the limitations of cross-sectional study designs, the causal relationship between GSH levels and caries activity remains unclear. Some conclusions even show contradictory findings (such as both positive and negative correlations between salivary GSH levels and caries severity). Future standardized cohort studies or interventional trials are needed to further elucidate the dynamic mechanisms of GSH in caries development, particularly in its regulatory role in oral microbiome balance. Additionally, the combined application of GSH with silver-based materials (such as silver diamine fluoride and silver nanoparticles) has shown potential in reducing tooth discoloration and enhancing antibacterial efficacy, which could become a promising minimally invasive anti-caries strategy. Future multicenter clinical studies are needed to clarify the dynamic changes of GSH and develop precise anti-caries strategies based on oxidative stress modulation.

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