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Polymeric Material as a Biomimetic Agent for Enamel Repair in Deciduous Teeth: An *In Vitro* Study

NISHATH SAYED ABDUL[1], ZEESHAN QAMAR[2*], NEDAL ABU-MOSTAFA[2], MOAATH AHMAD ALSAYEGH[2], MAY MOHAMMED ALSHEMAISI[2], RAHAF ABDURHMAN ALMOBTY[3], BASMA YAHYA[3], OUBADA SULIMAN[4], ABDULKARIM BASHA[5], OMAR MOHAMMED YOUSEF ALEIDI[6]

[1] Department of OMFS and Diagnostic Sciences (Oral Pathology), College of Medicine & Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia
[2] Department of O&MFS and Diagnostic Sciences, College of Medicine & Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia
[3] Department of Pediatric Dentistry, Ministry of Health, Riyadh, Saudi Arabia
[4] Department of Prosthodontics, College of Medicine & Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia
[5] Department of Preventive Dentistry, College of Medicine & Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia
[6] College of Medicine & Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia

Abstract: *Dental caries remains a significant health issue in pediatric populations, necessitating effective non-invasive treatments that promote remineralization and inhibit demineralization. This study investigates the efficacy of poly-γ-glutamic acid (PGGA), a natural biodegradable polypeptide, in preventing mineral loss and enhancing enamel repair in deciduous teeth. Study utilizing a pH cycling model mimicking oral environment showed that artificial caries lesions were treated with 1% and 2% PGGA with/without hydroxyapatite and compared to sodium fluoride (NaF) treatments. It was found that 2% PGGA markedly increased calcium uptake and integrated mineral recovery to a greater extent than some NaF concentrations. In-depth remineralization was evidenced by a cross-sectional microhardness study. These results advocate PGGA as an effective biomimetic material in the treatment of early childhood caries and a potential substitute for traditional fluoride therapies.*

Keywords: *Poly-γ-glutamic acid, deciduous teeth, remineralization, demineralization, dental caries, biomimetic material*

1. Introduction

Dental caries remains a major global health problem primarily driven by bacterial acids and it is a common disease among children. It causes enamel and dentin of teeth to lose minerals [1]. The prevalence of dental caries among young children is very high. Caries occurrence has been reported to be up to 71.9% in 5-year-old children in some areas. This means there is a need for better preventive and therapeutic approaches, as restoration only is not enough. Besides that, children are seen to develop caries rapidly, and that is why the limited care options to stop caries progression are not enough [2]. This urgent problem has led to a lot of research in new biomaterials and minimally invasive approaches to stop demineralization and encourage remineralization of the earliest stages of caries, which is still a big problem especially in deciduous teeth where caries tend to progress rapidly [3]. For example, bioactive restorative materials are attracting more attention because they are able to release fluoride, calcium, and phosphate ions, which in turn help to remineralize the neighboring carious lesions [4]. One biomaterial that is receiving a lot of attention as a possible candidate is poly-γ-glutamic acid (PGGA). It is a natural, biodegradable polypeptide with chelating and mineral-binding properties that make it highly effective in remineralization processes [2].

Pharmaceutical-grade fluoride remains the most effective, widely-used and trusted dental health product; however, if absorbed inappropriately it can lead to toxicity symptoms such as nausea

email: zeeshan.qamar@ymail.com

vomiting abdominal pain, diarrhea, and excessive salivation. This is why developing a potent, safe and biocompatible drug for children is still one of the most important research goals. PGA can also play a key role in enamel repair by stabilizing calcium and phosphate ions and subsequently promoting hydroxyapatite crystal formation as its polymer structure allows it to chelate metal ions [5].

The purpose of the present work was to examine the potential of PGGA acid treatment in protecting enamel by both reducing the rate of release of minerals and encouraging remineralization in primary teeth, that is why we are seeking an efficient material for caries treatment in pediatric dentistry. In detail, the goal of this paper is to analyse the impact of different PGGA concentrations alone and combined with the addition of hydroxyapatite on artificial caries lesions in primary teeth under the shell of simulated oral conditions. The experimental setup for this research will be a pH cycling model that reproduces 'both sides of the coin'—demineralization and remineralization phases—a necessary condition for the oral environment that is usually ignored in studies that use static models [6,7].

2. Materials and methods

2.1. Preparation of solutions and specimens

Stock solutions of 0.1 M acetic acid, sodium fluoride (NaF), and PGGA were freshly prepared and stored in sterile Thomas PP narrow-mouth bottles (Thomas Scientific, UK). All containers were autoclaved at 121°C and 15 psi for 15 min to maintain sterility and avoid microbial growth.

The 0.1 M acetic acid demineralizing solution was adjusted to pH 4.0 using a 1 M NaOH solution, and the final pH was verified with a calibrated pH meter [8]. Phosphate-buffered saline (PBS) was prepared according to the manufacturer's instructions (Oxoid, UK) by dissolving one tablet in 100 mL of deionized water. The solution was then autoclaved at 121°C for 10 min, its pH was corrected to 7.0 with NaOH, and it was used as the negative control.

PGGA, sourced from Poly-glu (Japan), was prepared at 1% and 2% (w/v) concentrations using deionized distilled water. Both formulations were adjusted to pH 7.0 to ensure stability. To promote mineral interaction, 2% hydroxyapatite (HAp) crystals (Plasma Biotal, UK) were added to each PGGA solution. The mixtures were stored at room temperature in sterile, airtight containers until required.

Sodium fluoride solutions at 0.1% and 0.5% (w/v) were prepared in deionized water and adjusted to pH 7.0 using the previously prepared 1 M NaOH. These concentrations were selected because they are commonly used in dental products and served as the positive control.

Ethical approval for the research was granted by the Riyadh Elm University Ethics Committee (FRP/2026/610/1474). A total of 25 sound primary human incisors were collected from patients at the Riyadh Elm University Dental Hospital after obtaining written informed consent. Any remaining soft tissue was removed by gentle scaling, and the teeth were rinsed thoroughly with distilled water before being stored in PBS at room temperature. No pre-treatment—such as acid etching or artificial demineralization—was performed before the experimental procedures.

2.2. Sample size calculation

The sample size was calculated prior to starting the study. Sample size calculation:

$$n = \left(\frac{Z_{1-\alpha/2} \times \sigma}{d} \right)^2$$

A minimum sample size was calculated to estimate the mean calcium loss with 95% confidence ($Z = 1.96$). Using an expected standard deviation of $\sigma = 0.40$ (from pilot readings) and an allowable margin of error of $d = 0.36$, the sample size was:

$$n = \left(\frac{1.96 \times 0.40}{0.36} \right)^2 = 4.74 \approx 5$$

Thus, 5 teeth were included in the experimental group.

2.3. Experimental design: assessment of de-/re-mineralization

To assess how PGGA and NaF influence enamel demineralization and remineralization, 25 primary incisors were coated with nail varnish, leaving a 2 × 2 mm^2 exposed window on the mid-labial surface to serve as the treatment area. The teeth were then randomly allocated into five groups (n = 5):

(i) 0.1 M acetic acid (negative control),
(ii) 1% PGGA + 2% HAp,
(iii) 2% PGGA + 2% HAp,
(iv) 0.1% NaF, and
(v) 0.5% NaF.

During the demineralization phase, all solutions were kept at pH 4.0. Each specimen was submerged in 0.1 M acetic acid for 24 h to create early enamel lesions. Calcium ion release was recorded every 15 min using a calcium ion-selective electrode (Ca^{2+} ISE).

Following demineralization, the teeth were placed in their assigned treatment solutions (PGGA + HAp or NaF, adjusted to pH 7.0) for 5 min. They were then transferred back into a mildly buffered acetic acid solution, adjusted to pH 6.0 with 1 M NaOH, for an additional 24 h to mimic remineralization conditions. Calcium ion concentrations were again measured, and the rates of mineral loss or gain were determined through linear regression. A positive slope indicated continued demineralization, whereas a negative slope reflected mineral uptake. The same specimens were later subjected to microhardness testing.

2.4. Scanning electron microscopy (SEM) analysis

The 2 × 2 mm^2 uncoated window on the mid-labial surface as the test site was scanned before (after demineralization at pH 4.0) and at the end of the experiment (remineralization at pH 6.0). Prior to the analysis the specimens were air-dried. Each sample was fixed on aluminum pin mounts to hold the specimen. Later same amount was used after treatment at pH 6.0 for the respective samples in order to maintain the position and location for pre- and post-treatment analysis.

2.5. Cross-sectional microhardness (CSMH) analysis

After completing the ion analysis, each tooth was thoroughly rinsed with deionized water. The primary teeth were then sectioned longitudinally through the lesion area using a precision diamond saw. Each half was embedded in epoxy resin so that the lesion surface remained exposed for cross-sectional microhardness assessment [8].

Cross-sectional microhardness (CSMH) was measured following the method originally described by Featherstone et al. [8], with a slight modification. Instead of the standard 50-µm spacing, indentations were placed at 25-µm intervals from the outer enamel surface to a depth of 250 µm. At each depth point, five indentations were made using a 25-g load with a 5-s dwell time. Mineral volume percentages were calculated for every depth, and the relative mineral recovery was determined by integrating the mineral content–depth profile using Simpson's rule, expressed as volume percent × enamel depth (µm). The finer 25-µm spacing was specifically chosen to better detect subtle subsurface remineralization changes in the PGGA-treated specimens.

3. Results

As the pH of the various acetic acid solutions was increased from 4.0 to 6.0 in the five acidi-fied treatment groups, the negative values for calcium ions with teeth indicated ion uptake by the teeth for the treatment groups in the following order: Calcium ion uptake rates (increasingly negative $R_{Ca}{}^{2+}$ values) were in the following order: Acetic acid (lowest) < 0.5% NaF < 0.1% NaF < 1% PGGA < 2% PGGA (highest). Nevertheless, the calcium ion uptake through the teeth in the acidified treatment groups was estimated for $R_{Ca}{}^{2+}$ through linear regression analysis and are shown in Table 1.

Table 1. Calcium uptake by teeth treated with different solutions. A negative control (acetic acid) and a positive control (0.5% NaF) were compared against lower-dose NaF and two concentrations of PGGA, all at pH 6.0

Treatment groups	R_{Ca}^{2+} uptake (mM/h) mean	Standard error
0.1 M acetic acid	-2.24×10^{-6}	$\pm 0.134 \times 10^{-6}$
0.1% NaF	-5.10×10^{-6}	$\pm 0.162 \times 10^{-6}$
0.5% NaF	-5.77×10^{-6}	$\pm 0.392 \times 10^{-6}$
1% PGGA	-5.30×10^{-6}	$\pm 0.346 \times 10^{-6}$
2% PGGA	-6.26×10^{-6}	$\pm 0.268 \times 10^{-6}$

The Z-test was used to analyze the R_{Ca}^{2+} uptake. It allowed for the statistical comparison of different treatment groups with a threshold of $\rho < 0.05$ for significance. The difference between the negative control and the four treatment groups was statistically signifi-cantly different (Table 1).

The calcium uptake rates (Mean ± SE, n = 5) demonstrated that most treatment groups showed statistically distinct outcomes ($\rho < 0.05$) during the second 24-h period. The sole exception was between 0.1% NaF and 1% PGGA, which were not significantly different from each other. Acetic acid and the two NaF concentrations served as the negative and positive controls, respectively.

The surface of teeth were later analyzed under SEM before treatment after demineralization at pH 4.0 and post treatment with the positive control 0.5% NaF (B) and experimental groups (2% PGGA (A) and 1% PGGA (C)) as shown in Figure 1. The teeth treated with 2% PGGA showed the paramount surface mineral deposition.

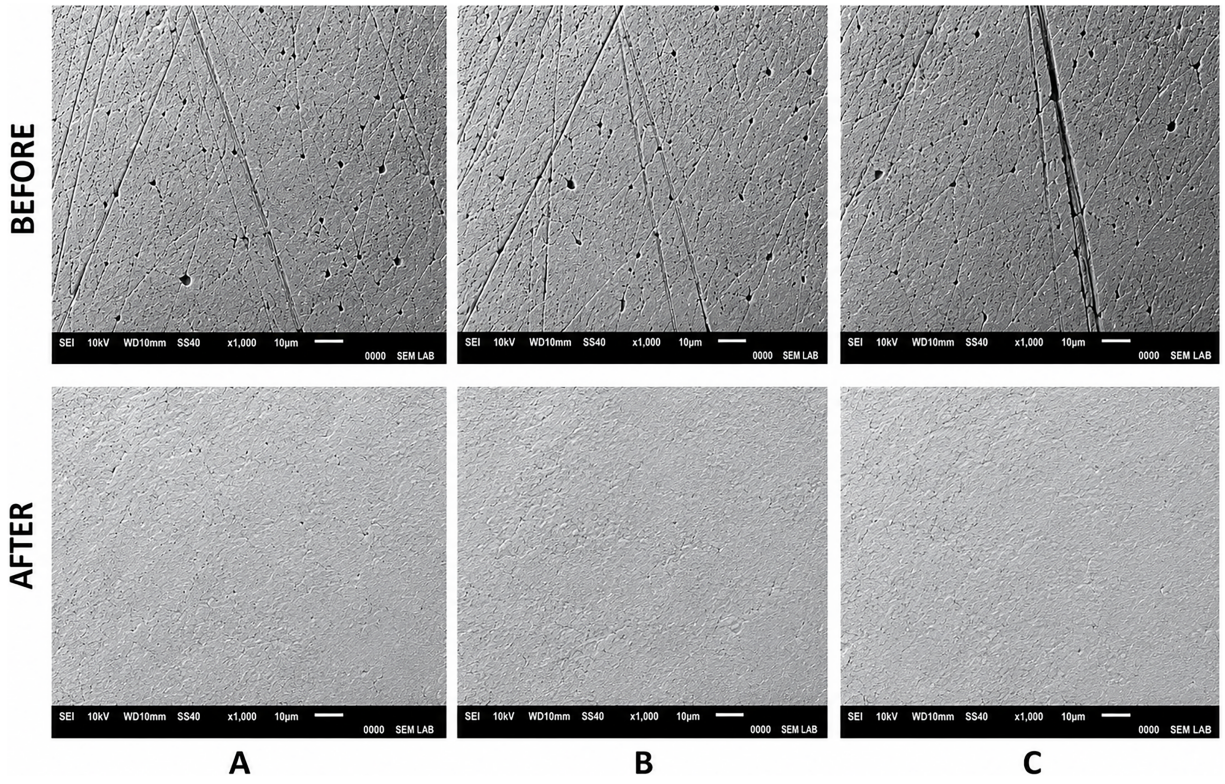

Figure 1. Scanning electron microscopic images of the tooth surface enamel on demineralization with pH 4.0 and later at pH 6.0. (A) Represent the teeth treated with 2% PGGA; (B) teeth treated with 0.5% NaF and (C) tooth treated with 1% PGGA solution

The CSMH of the teeth treated with various solutions at the end of the experiment with pH 6.0 acetic acid solution was evaluated at 25 µm in order to evaluate sub-surface remineralization. The 2% PGGA treated teeth in Table 2 have shown a strong potential for a sub-surface remineralization trailed by the gold standard solution of 0.5% NaF which extended upto the depth of 125 µm ($\rho < 0.05$). Whereas the sub-surface complete subsurface mineral recovery was not observed for the teeth treated 0.1% NaF and 1% PGGA.

Table 2. Enamel mineral density (by volume) measured after application of the respective treatment groups

Distance from tooth surface (µm)	Treatment groups				
	Acetic Acid	**0.1% NaF**	**0.5% NaF**	**1% PGGA**	**2% PGGA**
25	44.16 ± 0.3^{Aa}	73.07 ± 1.2^{Ab}	83.21 ± 0.5^{Ac}	73.12 ± 2.3^{Abd}	85.92 ± 0.7^{Ae}
50	42.17 ± 0.4^{Ba}	69.20 ± 1.1^{Bb}	84.13 ± 1.0^{Bc}	72.21 ± 1.3^{Bd}	85.05 ± 0.2^{Be}
75	48.09 ± 0.2^{Ca}	65.48 ± 0.5^{Cb}	82.71 ± 0.6^{Cc}	69.57 ± 0.5^{Cd}	84.39 ± 0.4^{Ce}
100	56.24 ± 0.5^{Da}	57.01 ± 1.1^{Db}	83.33 ± 1.4^{Ac}	62.77 ± 2.3^{DFd}	84.11 ± 0.7^{Ce}
125	67.21 ± 0.4^{Ea}	66.81 ± 0.5^{Eab}	82.83 ± 1.8^{Cc}	68.17 ± 1.2^{Ed}	82.93 ± 0.5^{De}
150	74.17 ± 0.2^{Fa}	76.17 ± 3.1^{Fb}	75.28 ± 1.4^{Dc}	75.98 ± 3.3^{EFbd}	83.77 ± 1.2^{Ee}
175	78.46 ± 0.7^{Ga}	79.03 ± 2.1^{Gb}	78.81 ± 1.8^{Eabc}	79.95 ± 2.9^{Fd}	83.79 ± 1.6^{Ee}
200	80.51 ± 0.5^{Ha}	82.11 ± 3.1^{Hb}	81.22 ± 3.2^{Fc}	83.01 ± 1.2^{Gbd}	82.68 ± 0.9^{FCbcde}
225	83.01 ± 1.3^{Ia}	83.08 ± 0.7^{Ia}	83.44 ± 1.1^{AGa}	83.03 ± 1.6^{Ga}	83.12 ± 1.7^{Fa}
250	82.97 ± 1.3^{IJa}	83.06 ± 1.9^{IJa}	83.21 ± 3.6^{AGa}	83.01 ± 2.3^{Ga}	83.29 ± 1.6^{FDa}

Note: Mineral content expressed in Mean ± SD where the number of determinants (n) is 5. $^{A–J}$Different capital letters mean statistical significant difference for mineral content value of same group at different depth ($\rho < 0.05$); $^{a–e}$Different lower case letter means statistical significant difference at same depth in different groups ($\rho < 0.05$). The individual experiment was carried out in heptalate. PBS was the negative control and NaF at three different concentrations was used as the positive control.

The data in Table 3 quantify the recovery of integrated mineral content in enamel following treatment with various acidified solutions. The results indicate that 2% PGGA was the most effective agent for promoting mineral recovery, whereas 0.1% NaF yielded the lowest recovery. A one-way ANOVA revealed a statistically significant difference in mineral recovery among the treatment groups ($\rho < 0.05$).

Table 3. Integrate mineral recovery value of enamel by the effect of various acidified solutions

Treatment groups	Integrated mineral recovery
Acetic Acid	8794.75 ± 134.24
0.1% NaF	12,472.80 ± 303.34
0.5% NaF	14,784.60 ± 351.24
1% PGGA	13,547.63 ± 322.82
2% PGGA	16,963.51 ± 242.19

Note: Integrated mineral recovery is presented as Mean ± SD (n = 5). The impact of the treatment groups on mineral content was statistically significant ($\rho < 0.05$). Experiments were performed in quintuplicate. Controls included PBS (negative) and two NaF concentrations (positive).

4. Discussions

Fluoride is considered as a benchmark treatment option, but due to its limitation and adverse effects for being used by the toddlers there is an emerging need for a biocompatible and biosafe material. The present study evaluated the potential of PGGA as a natural food derivative to inhibit demineralization and promote remineralization in deciduous teeth, contrasting its effects with established fluoride treatments [9]. Our findings indicate that PGGA, particularly at higher concentrations, exhibits superior remineralization capabilities compared to certain fluoride concentrations, aligning with recent advancements in dental material science aimed at enhancing restorative outcomes [10]. This aligns with broader research suggesting that novel biomaterials can provide effective alternatives or adjuncts to traditional fluoride-based therapies for dental hard tissue repair [11]. The observed trends in R_{Ca}^{2+} uptake and integrated mineral recovery suggest a dose-dependent effect for PGGA, where higher concentrations yielded more favorable results in mitigating demineralization and promoting enamel repair. This efficacy potentially stems from PGGA's chelating properties and its capacity to stabilize calcium and phosphate ions, thereby facilitating their deposition onto the demineralized enamel surface and enhancing the formation of hydroxyapatite crystals [10,12]. Such biomimetic remineralization strategies, which involve crystal nucleation on demineralized enamel, are increasingly recognized for their ability to restore the hierarchical microstructure of enamel [13,14].

Moreover, this biomimetic approach offers advantages over simple ion deposition by fostering structured crystal growth, which is crucial for restoring the mechanical integrity and acid resistance of the demineralized enamel [15]. The nuanced mechanism likely involves PGGA's ability to create a supersaturated environment of mineral ions while simultaneously acting as a scaffold for organized crystal growth, distinguishing its action from mere precipitation [16]. The incorporation of hydroxyapatite crystals into the PGGA formulations further augmented the remineralization process by providing nucleation sites, thereby accelerating crystal growth and mineral deposition within the enamel matrix, an approach supported by studies on other biomimetic agents [10,14]. The possible reason of PGGA outperforming 0.5% NaF formulation could be the polymeric structure binding larger number of Ca ions and promoting the apatite crystal formation at a faster rate than the positive control (0.5% NaF). The anionic –COOH group present in each glutamic acid residue possesses the ability to react with and bind to the cationic entity of another molecule or biopolymer, or it may act as or remain a free carboxylic acid. Consequently, PGGA acid is capable of dissolving especially Ca and Mg compounds to form stable ionic complexes [17]. In airways of the oral cavity displaying supersaturation, different free ions can be caught by PGGA, in particular the free Ca^{2+} which at pH conditions lower than those at which statherin is present can still bind and enhance remineralization. PGGA to the same extent as dental caries causing microbial flora (streptococcus mutans) it can resist by secreting a protective layer against the microbe. It can also resist the hydrolytic action of proteases [17,18]. This integrated strategy offers a promising pathway for pediatric dentistry, providing a non-toxic and biocompatible alternative to conventional fluoride treatments [19]. Future research should explore the long-term stability and clinical applicability of PGGA-based formulations *in vivo*, considering factors such as salivary flow, oral microbiome, and dietary influences on their sustained efficacy. PGGA being an extract of food product, shows potential to be used in various tropical options such as mouthwash, toothpaste and specially as an artificial saliva to protect the teeth from demineralization due to erosion or dental caries.

5. Conclusions

The findings from this study confirm that PGGA holds considerable promise as a natural, food-derived agent for combating dental demineralization and promoting enamel remineralization in deciduous teeth. Its demonstrated capacity to enhance mineral recovery and facilitate the structural repair of demineralized enamel suggests its potential as a valuable adjunct or alternative to conventional fluoride therapies, especially given its natural origin and biocompatibility.

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Author Contributions: Conceptualization: Zeeshan Qamar, Nishath Sayed Abdul. Methodology: Zeeshan Qamar, Nedal Abu-Mostafa, Abdulkarim Basha. Investigation: Nishath Sayed Abdul, Moaath Ahmad Alsayegh, May Mohammed Alshemaisi, Rahaf Abdurhman Almobty, Basma Yahya. Formal analysis: Zeeshan Qamar, Oubada Suliman. Resources: Abdulkarim Basha, Omar Mohammed Yousef Aleidi. Data curation: Moaath Ahmad Alsayegh, May Mohammed Alshemaisi. Writing—Original draft preparation: Nishath Sayed Abdul, Zeeshan Qamar. Writing—Review & Editing: Zeeshan Qamar, Nedal Abu-Mostafa, Abdulkarim Basha. Visualization: Oubada Suliman. Supervision: Zeeshan Qamar. Project administration: Zeeshan Qamar. Funding acquisition: Zeeshan Qamar. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Data is available on request.

Ethics Approval: The ethical approval was obtained from the Institutional Review Board of the Riyadh Elm University, Riyadh, Saudi Arabia (FRP/2026/610/1474). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their informed consent to participate in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

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