As a calcified tissue, dentin is composed of 70% mineral hydroxylapatite, 20% organic material and 10% water. Demineralization and remineralization process subject to each other in dentin during the whole life. In pathological conditions, demineralization outweighs remineralization when the biofilm caused by cariogenic bacteria on the tooth surface in a state of low pH for a long time. Resin-dentin bonding is another major reason for dentin demineralization. By penetration and entanglement of exposed collagen fibrils in the partially or completely demineralized dentin, the resin-dentin bonds are formed. In theory, all the exposed collagen fibrils should be permeated by resin which can seal the collagen fibrils and prevent the degradation of collagen fibrils. However it is impossible for the resin to displace water within the intrafibrillar and the intrafibrillar compartments of a demineralized collagen matrix, and infiltrate the collagen network completely.

Therefore, the remineralization of demineralized dentin is significant in improving the resin-bond stability of dentin.

Two different strategies have been applied for remineralizing demineralized dentin. Traditional strategy was based on the classical pathway of ion-mediated crystallization, or classical nucleation theory. This method depends on the existing apatite seed crystals in the dentin collagen matrix to attract calcium and phosphate ions and induces the epitaxial deposition. Hence, the remineralization does not generate in where seed crystals are absent like completely demineralized dentin. Although the classical nucleation theory can be employed in the remineralization of dentin, they achieved limited success in reproducing the structural hierarchy of intrafibrillar apatite deposition within the collagen matrix. Another strategy is the biomimetic remineralization which is particle-mediated and involves a mesoscopic transformation process. This bottom-up remineralization strategy does not rely on seed crystallites, even hybrid layers created by completely demineralized dentin can be remineralized.

The 20% organic material of dentin are mainly type I collagen (90 wt%) and non-collagenous proteins (NCPs). Type I collagen provides the three-dimensional structural framework in dentin remineralization and itself cannot induce nucleation of carbonated apatite from amorphous calcium phosphate (ACP) phases. NCPs are believed to play a crucial role in the remineralization of dentin. Dentine matrix protein 1 (DMP1) is comprised of NCPs which can hydrolysis into two parts. The N-terminal fragment of DMP1 can perform as the sequestration functional motif, the C-terminal fragment of DMP1 can induce the nucleation and growth of hydroxyapatite (HA), thus regulate the biomineralization of dentin. However, it is a great challenge to extract and purify DMP1 from dentin. For instance, there have been many studies using NCPs analogs like sodium tripolyphosphate (STPP) and polyacrylic acid (PAA) to mimic the dual functions of NCPs and achieve the biomimetic remineralization of dentin. Polyamidoamine (PAMAM) dendrimers are a kind of polymers with well-defined and mono-dispersed molecular structures. They have various functional end groups and topological architecture which allow many
alterations to be made to the surface of each dendrimer molecule\textsuperscript{28}. Moreover, PAMAM dendrimers exhibit greater biocompatibility and biomimetic properties, these endow PAMAM dendrimers with widely investigated as artificial proteins in biomimetic mineralization\textsuperscript{23,24}. It is demonstrated in our previous studies\textsuperscript{25}, that the carboxyl-terminated polyamidoamine dendrimer (PAMAM-COOH) could be immobilized within the collagen matrix and induce dentinal tubules occlusion. Meanwhile, it has been revealed that phosphorylated PAMAM dendrimers (PAMAM-PO\textsubscript{3}H\textsubscript{2}) could guide collagen fibrils realizing the intrafibrillar remineralization\textsuperscript{26}. However, PAMAM-COOH or PAMAM-PO\textsubscript{3}H\textsubscript{2} alone cannot reproduce the mechanical properties exhibited by natural mineralized tissues at the nanoscale level\textsuperscript{27,28}. Thus, we speculate that combing PAMAM-PO\textsubscript{3}H\textsubscript{2} with PAMAM-COOH can simulate DMP1 to induce intrafibrillar mineralization that resembles what has been perfected by nature. In this study, after the phosphate-terminated polyamidoamine dendrimer (PAMAM-PO\textsubscript{3}H\textsubscript{2}) could guide collagen fibrils realizing the intrafibrillar remineralization\textsuperscript{26,30}, G4 PAMAM dendrimers (Sigma-Aldrich, St. Louis, MO, USA) were firstly used to prepare the G4-PO\textsubscript{3}(OCH\textsubscript{3})\textsubscript{2}. The G4 PAMAM (0.800 g, 0.116 mmol) and paraformaldehyde (0.335 g, 11.160 mmol) were dissolved in the mixture of THF (5 mL) and KOH (0.5 mol/L) in a 100 mL flask. Dimethyl hydrogenophosphonate (1.032 g, 9.380 mmol) was added into the mixture. Then, the mixture was allowed to react at 70°C with vigorous stirring for 14 h\textsuperscript{5}. The product solution was evaporated to remove the excess organic solvent, then diluted with deionized water and transferred to a dialysis tube (MWCO3500) and dialyzed against deionized water for 1 day. The retentate solution was filtered through 0.45 um diameter membrane and lyophilized to obtain G4-PO\textsubscript{3}(OCH\textsubscript{3})\textsubscript{2}.

**Synthesis of G4-PO\textsubscript{3}H\textsubscript{2} dendrimer**

We synthesized the G4-PO\textsubscript{3}H\textsubscript{2} dendrimer in line with the method of Tomalia’s and Zhang’s classical strategies\textsuperscript{26,30}, G4 PAMAM dendrimers (Sigma-Aldrich, St. Louis, MO, USA) were firstly used to prepare the G4-PO\textsubscript{3}(OCH\textsubscript{3})\textsubscript{2}. The G4 PAMAM (0.800 g, 0.116 mmol) and paraformaldehyde (0.335 g, 11.160 mmol) were dissolved in the mixture of THF (5 mL) and KOH (0.5 mol/L) in a 100 mL flask. Dimethyl hydrogenophosphonate (1.032 g, 9.380 mmol) was added into the mixture. Then, the mixture was allowed to react at 70°C with vigorous stirring for 14 h\textsuperscript{5}. The product solution was evaporated to remove the excess organic solvent, then diluted with deionized water and transferred to a dialysis tube (MWCO3500) and dialyzed against deionized water for 1 day. The retentate solution was filtered through 0.45 um diameter membrane and lyophilized to obtain G4-PO\textsubscript{3}(OCH\textsubscript{3})\textsubscript{2}.

**Materials and Methods**

**Preparation of human tooth dentin samples**

Fifty-two sound human third molars were obtained and approved by the Ethics Committee of Guangxi Medical University, China and the Hospital of Stomatology of the school. The organic contaminants on the teeth were removed with a scalpel blade. The teeth were then treated with 3% sodium hypochlorite to remove bacteria and rinsed with phosphate buffered saline. The teeth were stored in 0.5% thymol at 4°C for no longer than 1 month prior to use\textsuperscript{29}.

All the teeth were cut perpendicular to the long axis of tooth, above the cement-enamel junction (CEJ), with a low-speed water cooled diamond saw (Isomet, Buehler, Lake Bluff, IL, USA). Each tooth was prepared into a 5×5×1 mm dentin specimen. A standard smear layer was created on both sides of the specimen, with the axis of tooth, above the cement-enamel junction (CEJ), for the coronal dentin surface for 30 s under running water. The smear layer was removed by using an ultrasonic cleaner (KQ3200DE, KunShang, Shanghai, China) for 10 min and then were demineralized with 0.5 M EDTA (pH 8.0) solution at room temperature for 72 h under shaking and rinsed with distilled water. The samples were thoroughly rinsed with deionized water for three times and ultrasonicated for 10 min to remove the stripped mineral. Further, the specimens were immersed in guanidine chloride (GuCl, 4 M) to remove the NCPs bonded mineral for 24 h. Finally, the specimens were rinsed with deionized water for three times and then ultrasonicated for 10 min. The samples were subsequently stored in thymol at 4°C before use. FT-IR (Spectrum One, PerkinElmer, Waltham, MA, USA), XRD (Dmax=1,400, 40 kV, 110 mA, Rigaku Denki, Tokyo, Japan), FE-SEM (SUPRA 55 SAPHIRE, Zeiss, Jena, Germany) and TEM (JEM 2100F, JEOL, Tokyo, Japan) were carried out to qualitatively characterize the demineralization degree of these dentin discs.

**Biomimetic remineralization**

A remineralizing solution simulated body fluid (SBF) is composed of \(136.8\, \text{mM NaCl}, 4.2\, \text{mM NaHCO}_{3}, 3.0\, \text{mM KCl}, 1.0\, \text{mM K}_{2}\text{HPO}_{4}, 3.0\, \text{mM CaCl}_{2}, 0.5\, \text{mM Na}_{2}\text{SO}_{4}\). Composite discs were made by set white Portland cement powder and...
This light-polymerizable hydrophilic resin blend can release calcium hydroxide (pH>9.25) to facilitate transformation of amorphous calcium phosphate (ACP) to carbonated apatite. Polyacrylic Acid (Mw 1800, Sigma-Aldrich; 1,000 ug/mL) and G4 PAMAM-COOH (Shandong, China; 1,000 ug/mL) were respectively added to SBF to stabilize ACP as nanoprecursors\textsuperscript{32,33}. The dentin discs were divided into three groups (as shown in Fig. 1). The remineralizing solution was changed every day. After remineralization, the dentin discs were washed three times with deionized water and ultrasonicated for 10 min. To characterize the remineralization effects, these dentin discs were firstly checked by XRD and were then characterized by FE-SEM, EDS (INCA350, Oxford company, Oxford, UK) and TEM.

RESULTS

Characterization of G4-PO\textsubscript{3}H\textsubscript{2}

\textsuperscript{1}H-NMR (Fig. 2A) shows that the area 2.630–2.645 ppm are the methylene protons of phosphate groups. It can be calculated that each G4-PO\textsubscript{3}H\textsubscript{2} has 42 phosphate groups on average. Figure 2B shows the FTIR spectra of unmodified and phosphorylated PAMAM dendrimers.

The data show that the peaks of 3,397.32 cm\(^{-1}\) and 1,539.25 cm\(^{-1}\) are due to amide vibration. The band at 1,046.66 cm\(^{-1}\) is attributed to the P-O adsorption peak of phosphate groups, which confirms the successful synthesis of G4-PO\textsubscript{3}H\textsubscript{2}.

Binding capability of G4-PO\textsubscript{3}H\textsubscript{2} and STPP to demineralized dentin

FTIR spectra of the demineralized dentin discs before and after phosphorylated with PAMAM-PO\textsubscript{3}H\textsubscript{2} and STPP are shown in Fig. 3. The resonances around 1,024.6 cm\(^{-1}\) which were assigned as phosphate groups. After the dentin discs were treated with neutral EDTA solution for one week, the resonances at 1,647.99, 1,556.01 and 1,247.19 cm\(^{-1}\), assigned as the amide I and amide II bands of type I collagen became more intense, while...
the phosphate group peaks are markedly weakened, indicating that the dentin discs were completely demineralized. After demineralized dentin discs were treated with PAMAM-PO₃H₂ dendrimers and STPP, phosphate group peaks re-appeared, indicating that these functional groups were introduced to collagen molecules. After 4 weeks of remineralization in remineralizing solution (Fig. 4), it still shows obvious phosphate group peaks which are distinctive for PAMAM-PO₃H₂ dendrimer and STPP. However, the characteristic peaks are not observed for demineralized dentin.

**Remineralization on demineralized dentin**

After being soaked in remineralizing solution for 4 weeks, the morphologies of the specimens were observed by SEM. As shown in Fig. 5b, after the dentin discs were demineralized in neutral EDTA solution for 1 week, the smear layer was removed, the dentinal tubules were opened and the collagen fibrils were completely exposed. For the dentin discs without PAMAM dendrimer and STPP treatment (blank group), there are little particles of regenerated minerals on the surface and in the tubule after being incubated for 4 weeks [Figs. 5(A1, A2)]. While the experimental group treated with PAMAM-PO₃H₂ and immersed in PAMAM-COOH remineralizing solution [Figs. 5(B1, B2)] exhibits effective mineral regeneration partially covering the surface of dentin and the dentinal tubule. When demineralized dentin discs were phosphorylated with STPP and immersed in PAA remineralizing solution (control group), demineralized collagen fibrils were mineralized and the dentinal tubule was filled with mineral [Figs. 5(C1, C2)].

EDS showed that the Ca/P ratio of regenerated minerals by PAMAM-PO₃H₂ and STPP are 1.11 and 1.25 respectively. The Fig. 6 performs the XRD results of the dentin discs surfaces before and after remineralization. Compared with the sound dentin, the peaks between 30° and 35° of demineralized dentin discs is broader and shorter, which indicates that the dentin discs were completely demineralized. The XRD result of the two groups of the remineralized dentin discs show the characteristic diffraction peaks of HA, with a peak corresponding to (002) at 2θ=26° and overlapping peaks corresponding to (211) at 2θ=32°. It is very similar to the XRD pattern of sound dentin.

After the dentin discs were demineralized in EDTA solution for 1 week, the TEM showed that the dentin samples were mainly composed of collagen fibers with

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**Fig. 4** The FTIR spectra of demineralized dentin with different treatment.

**Fig. 5** SEM images of the surfaces of sound dentin and EDTA demineralized dentin (a and b), SEM images after remineralization of blank group (A1, A2), experimental group (B1, B2) and control group (C1, C2) for 4 weeks.

**Fig. 6** The XRD spectra of sound dentin, EDTA demineralized dentin, blank group, control group and experimental group for 4 weeks.
obvious transverse striations and sparse fibers (Fig. 7). Four weeks after remineralization, the dentin discs were different from the demineralized dentin. Figure 8 shows the TEM results of blank group, experimental group and control group after 4 weeks of remineralization. In the blank group (A1, A2), there were no signs of ACP formation or remineralization, and the transverse features were still visible. At high magnification, the surface of A2 (×23,000) collagen fibers were smooth, with no apatite crystal found, and the transverse lines were obvious. In the experimental group (B1, B2), the deposition of apatite crystals was observed between the collagen fibers, and the transverse pattern characteristics were seen in the partially mineralized collagen fibers. At high magnification, a blurred transverse pattern could be seen in the partially mineralized collagen fibers of B2 (×23,000), and the collagen matrix was sparse. However, the high magnification view showed that the horizontal features cannot be identified. In the control group (C1, C2), there were more apatite crystals. At high magnification, C2 (×23,000) showed that the collagen matrix gradually became dense due to the deposition of apatite crystals. Some of the collagen with a higher degree of mineralization can be seen as crystal deposition (as shown by the white arrow). It may be that the transverse grain characteristics of collagen fibers are not obvious because of the high mineralization density.

DISCUSSION

The capacity of binding strength to the dentin is very important for the biomineralization analogs to realize remineralization. When the ability of biomineralization analogs to combine with demineralized dentin is insufficient, it cannot induce remineralization. The FTIR spectra shows that the characteristic phosphate group peaks of dendrimer are obviously detected on demineralized dentin after 24 h PAMAM-PO₃H₂ and STPP coating and rinsing with deionized water three times. After 4 weeks biomineralization, the dentin discs with PAMAM dendrimer and STPP treatment still apparent clear characteristic phosphate group peaks (1,026.40 cm⁻¹). The results suggest that the collagen fibers were phosphorylated. The collagen matrix was coated with PAMAM-PO₃H₂ and STPP and become phosphorylated. The surface of collagen matrix were gathered around numbers of phosphate anions, which will react with calcium ions to induce minerals deposition³⁴. Same results also shown in our previous report²⁵ and other report²⁶, which indicate that the PAMAM-PO₃H₂ and STPP have excellent binding strength to demineralized dentin to resist saliva and food so it can fulfill apatite nucleation. Studies have found that biomineralization should be a matrix particle-mediated process rather than rely on existing seedapatite crystallites and an ideal biomineralization happen when both interfibrillar and intrafibrillar remineralization occur at the same time³⁵. In nature, the DMP1 is responsible for stabilization of ACP and mineral formation and can perfectly induce the two processes of remineralization³⁶. In this study, G4-PO₃H₂ and G4-COOH are investigated as the dual DMP1 analogs to induce both interfibrillar and intrafibrillar remineralization of completely demineralized human dentin.

By XRD of the specimens, the diffraction pattern of the regenerated crystals is analyzed to obtain the type and the structure. After 4 weeks incubation, the XRD patterns indicate that HA crystals are formed with the help of G4-PO₃H₂ and STPP. While the specimens without treatment exhibits no obvious characteristic peak of HA crystals. However, the two groups did not show the same characteristic peak as the XRD pattern of the intact dentin. This may suggest that although the HA crystals were formed, while the formation of the quantity is less, the characteristic diffraction peaks appearing were not obvious. As we all known, the Ca/P ratio of HA of sound dentin is 1.67. Compared with experimental group, the result of control group (1.25) was closer to sound dentin. On the contrary, the blank group without dendrimer and
STPP treatment cannot obtain obvious remineralization, which to a certain extent reflects the appearance of new calcium after remineralization of PAMAM-PO$_3$H$_2$ and STPP. The results also indicate that the G4-PO$_3$H$_2$ and G4-COOH have great potential to guide the dentin remineralization.

FE-SEM and TEM can show the changes of dentin microstructure before and after remineralization. FE-SEM can obtain the ultrastructure information of the surface ultrastructure of samples with a strong stereoscopic sense of faithful original appearance. For the dentine samples without PAMAM dendrimer and STPP treatment, after 4 weeks of remineralization, it was found that the surface and the tubules of the samples were only partially covered with mineral as collagen matrix itself can inhibit the mineral remineralization, which is consistent with previous report. The few deposition of minerals should be attributed to the remineralizing solution that full of free calcium and phosphate ions. The group incubated with PAMAM-remineralizing solution that showed effective mineral deposition of minerals should be attributed to the remineralization, which is consistent with previous report. The few deposition of minerals should be attributed to the remineralizing solution that full of free calcium and phosphate ions. The group incubated with PAMAM-COOH and PAMAM-PO$_3$H$_2$ showed effective mineral regeneration only not on the surface of dentin but also in the dentinal tubule. While compared with the STPP and PAA group, the surface of the samples is fully covered with mineral deposit as that of sound dentin. It is hard to find the dentinal tubule as the tubules are full of newly generated minerals. The preparation of the observed samples of TEM need to be made into 70 nm thick by the ultrathin section mechanism. Therefore, it can be used to observe and detect the internal ultrastructural changes of dentin collagen fibers after remineralization. The TEM images of the blank group without any treatment showed that after 4 weeks of remineralization, no apatite crystals were formed at the collagen fibers, and the PAMAM-PO$_3$H$_2$ showed effective mineral regeneration only not on the surface of dentin but also in the dentinal tubule. While compared with the STPP and PAA group, the surface of the samples is fully covered with mineral deposit as that of sound dentin. It is hard to find the dentinal tubule as the tubules are full of newly generated minerals. The preparation of the observed samples of TEM need to be made into 70 nm thick by the ultrathin section mechanism. Therefore, it can be used to observe and detect the internal ultrastructural changes of dentin collagen fibers after remineralization. The TEM images of the blank group without any treatment showed that after 4 weeks of remineralization, no apatite crystals were formed at the collagen fibers, and the PAMAM-PO$_3$H$_2$ showed effective mineral regeneration only not on the surface of dentin but also in the dentinal tubule. While compared with the STPP and PAA group, the surface of the samples is fully covered with mineral deposit as that of sound dentin. It is hard to find the dentinal tubule as the tubules are full of newly generated minerals.

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DMP1 is an acidic noncollagenous protein played significant role in the mineralized matrix of both dentin and bone. It has a high content of glutamic acid and aspartic acid residues, suggesting that it would have a very high capacity for binding calcium ions. DMP1 is cleaved to a 57 kDa C-terminal polypeptide and a 37 kDa N-terminal polypeptide. The C-terminal of DMP1 are spatially organized in a form that specifically complements the crystallography of the calcium phosphate nuclei. Study have found that the aspartic acid residues at the N-terminus of DMP1 can bind calcium ions strongly, favoring mineral formation and stabilization. Thus, DMP1 could serve dual roles during dentin remineralization: to inhibit crystal growth and to prevent further calcium phosphate nucleus growth by stabilizing nanoclusters and promoting controlled mineral nucleation when immobilized on self-assembled collagen templates. Liu has reported a polyphosphate-based biomimetic collagen mineralization strategy which used a low molecular weight PAA to replicate the functional motif of the N-terminal fragment of DMP1, and a small inorganic STPP to replicate the functional motif of the C-terminal fragment of DMP1. The results showed that the hierarchical intrafibrillar mineralization of a collagen matrix occurred when PAA and STPP were combined. Besides, Wang et al. used the PAMAM-PO$_3$H$_2$ and PAA to accomplished the remineralization of totally demineralized dentinal collagen fibers. The ACP was stabilized by PAA and infiltrate into collagen fibers, then the apatite nanocrystals induced by PAMAM-PO$_3$H$_2$ would grow to larger crystal along the surface of the collagen fibers. Hence, we speculate that the main groups of STPP and PAA induced dentin biomimetic remineralization are the phosphate group of STPP and the carboxyl group of PAA. However, both are linear small molecular, and PAA has certain cytotoxicity and cannot be used in vivo. The modified PAMAM polymer is a spherical macromolecule with a three-dimensional structure. The molecules of G4 PAMAM-PO$_3$H$_2$ and PAMAM-COOH are 1.47 kDa and 1.01 kDa, respectively. Molecules larger than 40 kDa are completely excluded from these internal water compartments of type I collagen, while molecules smaller than 6 kDa can diffuse into all the water compartments within the collagen fibril. Thus, it is practicable that PAMAM-PO$_3$H$_2$ and PAMAM-COOH can easily penetrate and displace water from collagen fibril.

In the present study, we use the phosphorylated PAMAM dendrimers combined with carboxylated PAMAM to induce the remineralization of fully demineralized dentine in the remineralization solution successfully. In the amorphous precursors induction step, the metastable ACP was small enough to penetrate in the demineralized collagen matrix with the help of PAMAM-COOH and PAA. The PAMAM-PO$_3$H$_2$ and STPP play the role of inducing the nucleation and growth of HA. However, with the absence of these DMP1 analogs, there was very limited promotion of the mineralization of collagen fibers. Although the PAMAM-PO$_3$H$_2$ and PAMAM-COOH can induce the remineralization between collagen fibers in demineralized dentin to some extent, its induction ability is not as good as that of the STPP and PAA group. The reason, on the one hand, may be that although the modified dendrimer PAMAM can bind a large number of functional groups, such as G4-COOH has 64 carboxyl groups and G4-PO$_3$H$_2$ has 42
phosphate groups, the group in which it functions may not have more groups of STPP and PAA in the control group; the other reason may be that the concentration of STPP and PAA applied to remineralization in the control group is the most appropriate induced concentration, the STPP concentration is 2.5%, while the PAA concentration is 1,000 μg/mL, the concentration in the experimental group is consistent with the control group. This concentration may not be the optimal concentration for PAMAM-PO₃H₂ and PAMAM-COOH for biomimetic remineralization. The next step is to study the adequate concentration of mineral dentin bionic remineralization of the PAMAM-PO₃H₂ and PAMAM-COOH.

CONCLUSION
In this study, G4-PO₃H₂ is successfully synthesized and together with G4-COOH could act as the biomimetic analogs of noncollagenous proteins and be employed in the remineralization of totally demineralized dentin. Phosphorylated PAMAM and carboxylic PAMAM dendrimers may have great potential in clinical treatment of demineralized dentin.

ACKNOWLEDGMENTS
This work was supported by the Natural Science Foundation of China [Grant Number 81760204].

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