Journal of Pharmaceutical Research International

32(25): 19-28, 2020; Article no.JPRI.61573
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Future Perspectives of Biomimetics in Restorative Dentistry

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NB and MMM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NB and MMM managed the analyses of the study. Author SM managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i2530820
Editor(s):
(1) Dr. Mohamed Fathy, Assiut University, Egypt.
Reviewers:
(1) Farid Bourzgui, Université Hassan II, Morocco.
(2) Ebtissam M. AL-Madi, King Saud University, Saudi Arabia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/61573

Review Article

Received 27 July 2020
Accepted 03 October 2020
Published 20 October 2020

ABSTRACT

The main goal of tooth restoration aims at achieving mineralization of initial enamel and dentinal lesions in native form. Most of the restorative materials and remineralization adjuvants for enamel and dentin mineralization are evidenced in the literature. Although commercially available restorative materials exhibit superior esthetics, mechanical properties and cost effectiveness, durability of the restoration threatened by the occurrence of inadequate strength, long-term solubility, and weaker adhesion to tooth and accelerated degradation after being bonded to tooth structure. Recently, the role of biomimetic science in restorative dentistry aims at creating a restoration that can be highly compatible with the structural, functional and biologic properties of dental tissues to reproduce and emulate the original performance of the intact tooth with high durability. In order to recover the prismatic structure in mineral-depleted enamel and to achieve interfibrillar mineralization in dentin, non-collagenous protein analogues have been proposed as templates for apatite deposition. Biomimetic analogues must be necessary to achieve functional mineralization and to recover the dynamic mechanical properties of teeth. The use of these analogues associated with ion-releasing materials seems to be a promising approach for both

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enamel and dentin remineralization. This review enlightens the current and future perspectives of biomimetic analogues used for enamel and dentin remineralization as the clinical translation of this biomimetic research can be considered as the boon to restorative dentistry.

Keywords: Dentin remineralization; enamel remineralization; functional remineralization; biomimetic remineralization; biomimetic analogues.

1. INTRODUCTION

From the beginning of mankind, humans have been inspired by principles of nature. The act of 'copying' the nature and giving 'life like', which imitates the nature is called as Biomimetics or biomimicry [1]. Biomimetics is the study of formation of structure or function of biologically produced substances and materials and its biological mechanisms for the purpose of synthesizing similar products by artificial mechanisms that mimic natural structures [2].

The role of biomimetic science in restorative dentistry aims at creating a restoration that is highly compatible with the structural, functional and biologic properties of dental tissues to reproduce and emulate the original performance of the intact tooth. The concept of just "drill and fill" is changed to the application of physical and mechanical tests combined with fundamentals of engineering science to design the restorative materials to simulate the native tissue. Thus the field of restorative dentistry has come a long way from just restoration of cavity to the concept of regenerating the enamel or dentin or the whole tooth itself [3].

Many restorative materials are commercially available with superior esthetics, mechanical properties and cost effectiveness. However durability of these restorations can be often compromised by occurrence of inadequate strength, long-term solubility, weaker adhesion and accelerated degradation after being bonded to tooth structure, fracture leading to secondary caries, and pulp necrosis [4]. While there are enormous development and improvement in the material aspect, no material has the ability to restore back the natural structural architecture of enamel and dentin which accounts for regaining the complete dynamic mechanical strength of the tooth [5]. The future of successful restorative dentistry lies in the emergence of material with remineralization or regeneration capacity of the lost tooth structure with resistance to further degradation. Current researches on enamel and dentin remineralization are focussed on the quality of apatite precipitation in the demineralized tissue. Biomimetic restorative materials can play a vital role in guiding the mineral deposition in order to restore the tissues to its native structure, organization and functionality. Thus, the ideal properties of biomimetic restorative material should be as follows:

- Maintain as much natural tooth structure as possible.
- Mimic or form natural enamel and dentin
- Absorb and distribute stress like tooth structure and
- Improve durable bond with natural tooth structure.

Biomimetic science is an emerging concept that helps to focus the dental research on simulating the nature and translate this scientific knowledge into future clinical treatments. This review enlightens the current and future perspectives of biomimetic science used for enamel and dentin remineralization.

2. BIOMIMETIC STRATEGY FOR ENAMEL RESTORATION

The acellular enamel does not regenerate itself unlike other bio-mineralized tissues in the body (dentin and bone) [6]. Traditional restorative materials such as amalgam, GIC or composite resin are used to substitute the lost enamel but none of these materials could achieve the exact physical, mechanical, and aesthetic properties of enamel [7]. The concept of incorporating remineralizing agents in restorative materials to reinforce the tooth has also been tried. However, the lack of ability to guide the formation of hydroxyapatite crystals to have ordered mineral architecture under physiological conditions is still questionable with conventional materials. Therefore, there is a need for an alternative approach that can safely and effectively promote organized mineral deposition onto the underlying tissues.

Dental enamel is a unique mineralized substance which mainly comprises of 96% hydroxyapatite and 4% breakdown products of organic component of non-collagenous proteins(NCPs). Approximately 90% of these NCPs are

amelogenins [8]. These NCPs acts as a key factor in controlling the oriented elongation of enamel rod growth during the mineralization process and responsible for guiding the deposition of hydroxyapatite in its characteristic prismatic structure. These are negatively charged structure that interacts with calcium ions to control the orientation of the growing crystals [9,10]. Remineralization and regeneration of enamel can be possible to a certain extent, by the use of biomimetic template analogues of the natural proteins involved in bio-mineralization [11].

Although the calcium and phosphate ions in the saliva permit the recovery of mineral lost, amorphous calcium phosphate (ACP) has been proposed to be an essential precursor phase during the formation of mineralized tissue [12]. ACP is an unstable component than its crystalline polymorphs of calcium phosphate, which can readily dissolve and converts to HAP in aqueous solution**.** The role of NCPs which are secreted by ameloblast during the secretory stage of amelogenesis, particularly *amelogenin*, [13] has been believed to play an important role in the stabilization of ACPs and to control the crystal growth, including its size, shape, and organization during enamel biomineralization. In addition, the guidance for hierarchical structural assembly of HAP can be achieved with the help of *protein peptide* [14]. The peptide may act as Ca^{2+} carrier as well as regulating factor. The stabilized calcium and phosphorus ions, binds with the peptide and become biologically available for the remineralization. It has been regulated by the NCPs to transform into *ordered hydroxyapatite crystals.*Thus the development of natural protein analogues which could substitute amelogenin and imitate the process of biomineralization would be an effective strategy to restore enamel in its original form. Thus the main requirements of functional remineralization of enamel are: 1. ACP precursor/ source 2. Amelogenin analogue 3. Protein peptide. The combination of non- classical crystallization mechanisms and development of synthetic amelogenin analogues, thereby emulating remaining biomineralization steps can serve for future trends to improve the repair of initial enamel defects. There are many biomimetic systems developed recently with various protein analogues which serve the function as follows:

2.1 Amelogenin [15]

It promotes the oriented bundle formation and also mediate the formation of orderly enamel-like structure. It has the control over the organized growth of apatite crystals and form transitional complexes with ACP. It promotes the hydrolysis of ACP to stable HAP by stabilizing the Ca-P clusters and guide their arrangement into linear chains.

2.2 Enamel Matrix Protein [16]

It guides the continuous growth of crystals and prevents the fusion of premature crystals thereby controlling nucleation, growth of the crystals, morphology and subsequent elongation.

2.3 Polyamidoamine Dendrimers (PAMAM) PAMAM-COOH, ALN-PAMAM-COOH, PAMAM-PO_3H_2 [17,18]

It absorbs onto the etched enamel surface and provide nucleation sites and mineralization template for HAP. The phosphate-terminated dendrimer has been shown to be capable of forming HA layer of 11.23μm thickness on the acid-etched tooth enamel with crystals oriented along Z-axis, when treated with in artificial saliva for 3weeks. Alendronate-conjugated dendrimer regulates the growth of crystals and induces nanorod-like HAP with high uniformity. It also showed a recovery of 95.5% hardness of the enamel which makes a promising biomimetic material as well as potential remineralizing agent for etched enamel.

2.4 3DSS [19,20]

It forms 3D biomimetic scaffolds capable of nucleating HAP and has a high affinity to bind with the HAP surface. It promotes HAP with a small average crystalline size and induces formation of stable ACP nano-precursors preventing them from aggregation and precipitation.

2.5 Glutamic Acid [21]

It induces the nano apatite assembly on enamel and induces the oriented aggregation of nanoapatite and provides the active sites to control enamel formation. It has strong calcium complex forming potential in high concentration. The orientation of crystals mimics the natural enamel rod direction with the packs of crystals tightly arranged in a “fish-scale” manner proving its biomimetic ability to form enamel.

2.6 Polyacrylic Acid [22]

It sequester calcium and phosphate ions and forms amorphous calcium phosphate nano-precursors. It was shown to improve the microhardness of enamel when treated onto artificial lesion,with enhanced mineralization, mechanical properties and higher phosphate content in combination with bio active glass.

2.7 Phosphorylated Chitosan (Pchi-ACP) [23]

It binds calcium ions, initiates nucleation and stabilizes ACP to form the nano-complexes of Pchi-ACP. It get adsorbs onto the surfaces of HAP crystals and shows similar remineralization of enamel lesions to that of fluoride, with higher remineralizing rate. It is a natural analogue which can be used as potential remineralizing agent for incipient lesion of enamel.

2.8 Casein Phosphopeptide [24]

It stabilizes calcium, phosphate and hydroxide ions and prevents spontaneous precipitation of calcium phosphate and it has proven to promote enamel subsurface lesion remineralization. It can also maintain the gradient of ions in high concentration on subsurface lesion along with high rate of remineralization.

3. RECENT STUDIES ON ENAMEL BIOMIMETIC REMINERALIZATION SYSTEMS

In recent years, treatment of caries lesions by the application of different combinations of biomimetic systems has been ACP based systems though repair and prevention of initial enamel lesions have not yet been confirmed in clinical trial.

- An electrospun hydrogel mat of ACP/PVP (poly(vinyl pyrolidone)) nanofibers was shown to aid in transformation of the spherical ACP phase in situ at the surface of the enamel to produce a contiguous layer of crystalline fluoridated hydroxyapatite with approximately 500 nm thickness [25].
- Nano-sized HAP particles are also experimented to repair initial submicrometer enamel erosions. HAP with a size of 20 nm adsorbed strongly to the enamel surface and reinforced the acid-etched enamel surface [26].
- An anionic peptide P11-4 (Ace-Gln-Gln-Arg-Phe-Glu-Trp-Glu-Phe-Glu-Gln-Gln-NH2) has potential to introduce apatite mineralization to caries-like lesions by facilitating the subsurface regeneration of the enamel lesion by supporting de novo mineralization and by nucleating hydroxyapatite in a similar mode of natural formation of enamel. Assembled P11-4 forms scaffold-like structures with negative charge domains, mirroring biological macromolecules in mineralized tissue extracellular matrices. Class V lesions treated with a single application of P11-4 showed improvement in size and progression which was maintained even after 180 days post-treatment on initial caries lesions [27].
- Li et al. fabricated an anionic oligopeptide amphiphile OPA (C18H35O-Thr-Lys-Arg-Glu-Glu-Val-Asp) that contains the hydrophilic functional domain of amelogenin to initialize hydroxyapatite nucleation and promote biomimetic mineralization of demineralized enamel. It was shown that apatite crystals were formed on the etched enamel after treatment with OPA peptide. [28]
- 8DSS: A peptide carrying 8 repeats (8DSS) has been shown to promote mineral deposition onto human enamel and improve the surface properties of demineralized enamel both in in-vitro and in-vivo studies. 8DSS showed significantly higher mineral content with definitive change in surface morphology from elongated hydroxyapatite nanorods in the demineralized enamel to nanoscale flakes. It also enhanced the mechanical properties, hardness and elastic modulus of demineralized enamel. Furthermore, it promoted the uniform nano-crystallization of calcium phosphate carbonate over the surfaces, thereby reducing the surface roughness of enamel [29].
- PAMAM-based dendrimers: PAMAM dendrimers and phosphate-terminated dendrimer (PAMAM-PO_3H_2) showed the ability to remineralize acid-etched human tooth enamel. It has strong tendency to self-assemble into hierarchical structures such as the preferential orientation of the c-axis of the HAP crystals along the amelogenin aggregates. Alendronate-conjugated PAMAM dendrimer (ALN-PAMAM-COOH**)** also induces in situ remineralization of tooth enamel due to the combined effect of the

HA-anchored property of the ALN moiety and the remineralization capability of the –COOH moiety [17,18].

- Amelogenin-releasing agar hydrogel: Repetitive application of amelogenin-releasing agar hydrogel containing calcium, phosphate, and fluoride was evaluated to remineralize etched enamel in a cyclic treatment model and multispecies oral biofilm model. It significantly improved enamel hardness continuously over time and offered promising possibility of remodeling complex enamel minerals in an amelogenin-containing system [30].
- CS-AMEL hydrogel: Development of a new amelogenin-containing chitosan (CS-AMEL) hydrogel significantly improved in situ regrowth of apatite crystals, generated a robust enamel–restoration interface, which is important for ensuring the efficacy and durability of restorations. Amelogenin assemblies carried in chitosan hydrogel could stabilize Ca–P clusters and arrange them into linear chains, which fuse with enamel crystals and then develop into enamel like co-aligned crystals with potential antimicrobial activity of chitosan [31].
- Leucine-rich amelogenin peptide (LRAP): LRAP is a 59-residue splice variant of amelogenin and contains the N- and C-terminal charged regions of the full-length amelogenin. LRAP, like full-length amelogenin, also has a great potential for biomimetic regrowth of tooth enamel. LRAP selectively promotes linear growth along the c-axis of enamel crystals. It could stabilize ACP and guide ACP transformation into ordered bundles of apatite crystals [32].
- Chitosan based systems :

- Synthetic hybrid chitosan (CS)-hydroxyapatite (HAP) - Chitosan causes major morphological modifications, subtle changes in HAP. CS macromolecules act as matrix for orderly embedding the structured amelogenin-HAP nanocrystals by selectively binding Ca^{2+} from HAP faces via coordination interactions and amelogenin molecules adsorbed onto hydrophobic contacts [33].
- HAP@ACP Nanoparticles Guided by Glycine: CMC-ALN matrix stabilizes amorphous calcium phosphate (ACP) to form CMC/ACP nanoparticles. Sodium hypochlorite decompose amelogenin in vivo to degrade and generate HAP@ACP core-shell nanoparticles. HAP@ACP, which on the introduction of Gly lead to subsequent formation of oriented mineral crystal bundles orderly which transform from an amorphous phase to well-ordered rod-like apatite crystals [34].

  Chimaeric peptide-mediated nanocomplexes of carboxymethyl chitosan/amorphous calcium phosphate (CMC/ACP) guided by amelogenin also can transform into enamel-like crystals which tightly bounds onto the demineralized surface. The newly formed enamel-like crystals were nearly well-organized with strong mechanical properties [35].

- Other enamel biomimetic systems

  Other biomimetic systems such as glycerine-enriched gelatin system agarose hydrogel system (30), CS-EMD hydrogel [31] multifunctional biomimetic CS-HAP has been used to form layers containing ordered enamel-like structures of fluoride-substitute hydroxyapatite microcrystals on a human enamel surface using ethylene diamine tetra acetic acid disodium salt dehydrate (EDTA) as the mediating agent. Under near-physiological materials, it could provide highly organized enamel-like structure for teeth remineralization conditions [36].

4. BIOMIMETIC STRATEGY FOR DENTIN RESTORATION

Dentin is a more complex structure than enamel. The matrix composition consists of mineralized tissue with proteinaceous content by almost 50% in volume and comprised of collagen fibrils. The mineral phase in dentin can be described as intrafibrillar mineral which confines within or immediately adjacent to the gap zones of the collagen fibrils and interfibrillar mineral which has been located within the interstitial spaces separating the fibrils [37].

The mechanical properties of dentin are largely driven from its intrafibrillar mineralization. Apatite mineral in dentin needs to be bound and/or structurally incorporated in between the collagen fibrils to mechanically reinforce the dentin in terms of elastic modulus, hardness, and compressive strength [38]. Dentin remineralization is less effective than enamel remineralization on using conventional fluoride therapies and other enamel remineralizing agents [39]. Remineralization of partially-demineralized dentin with conventional dentin remineralization strategy such as calcium

hydroxide, Mineral Trioxide Aggregate and other calcium silicate based materials cannot provide complete remineralization within hybrid layers or the superficial part of a caries-affected dentin lesion due to the fewer amounts of residual mineral crystals. Also remineralization cannot occur in locations where seed crystallites are absent [40]. Thus, there can be no intrafibrillar apatite deposition expected from conventional top-down mineralization approach.

5. NON-CLASSICAL CRYSTALLIZATION PATHWAY

This is a multistage process (Bottom Up approach) [40]. Characterized by the self-assembly of amorphous nano-precursor particles and their subsequent mesoscopic transformation in biomineralization. Initially, the calcium and phosphate ions self-assemble into pre-nucleation clusters in the presence of calcium and phosphate source. Following this, these pre-nucleation clusters aggregate into amorphous ACP nano-precursors by the influence of NCP and its peptide component. These nano-precursors have the ability to penetrate into the gap zones of collagen fibrils and further crystalize into apatite along the intrafibrillar space of collagen. The intrafibrillar remineralization of collagen fibrils results in interfibrillar remineralization between adjacent collagen fibrils. Apatite mineral in dentin needs to be bound to the collagenous matrix or ideally be incorporated into the collagen fibrils to mechanically reinforce the tissue. Thus, process-directing agents along coupled with NCP analogue on remineralization agents can only induce intrafibrillar mineral deposition in collagen [10].

5.1 NCP Analogues

As collagen matrix serves as a scaffold for crystal deposition in dentin with lack of nucleation for hydroxyapatite deposition, the biomimetic remineralization process can be modulated by a series of NCPs. Thus, current research focuses on developing the NCP analogues which can play a vital role in biomimetic remineralization of dentin. The role of NCPs analogues are as follows:

- They have high affinity for calcium ions and collagen fibrils.
- They can act as modulator of elegant hierarchical structure of dentin.
- They bind to collagen matrix, and induce ACP nano-precursors into collagen matrix.
- They stabilize ACP precursors.
- They mainly regulates biomineralization of dentin by acting as a nucleator or inhibitor.

Some of the commonly tried NCP analogue systems are mentioned as follows:

5.2 Polyacrylic Acid and Polyvinylphosphonic Acid (PVPA) [41,42]

PAA simulates $CaPO_4$ binding sites of DMP1 and stabilizes ACP. It also helps in inhibiting nucleation for ACP stabilization and prolongs the lifetime of ACP. PVPA also can simulates the collagen-binding function of DMP1and inhibits the activity of MMPs. It also helps in recruiting ACP nano-precursors into collagen matrix. PAA and PVPA together, the nanoprecursors binds to the acid-demineralised collagen matrix and forms poly electrolyte-stabilised apatite nanocrystals initiating intrafibrillar and interfibrilllar remineralisation in collgen. The remineralization occurs through bottom up approach from mesocrytals to nanocrystal formation, thereby proving them to be a promising biomimetic component for guided remineralization in dentin.

5.3 Sodium Trimetaphosphate (STMP) [43]

STMP has phosphate groups which get adsorbed on demineralized collagen under an alkaline pH. It phosphorylates type I collagen and binds to demineralized collagen matrix forming covalent bonds. Studies have shown that STMP can remineralize resin-bonded dentin with intrafibrillar deposition of nanoapatite around phosphorylated collagen. It also attracts ACP-nanoprecursors by electrostatic force to initiate nuclei of crystallization within the gap zones of collagen fibrils.

5.4 Phosphorylated Chitosan (P-Chi), Carboxymethyl Chitosan/Amorphous Calcium Phosphate (CMC/ACP) [44]

It binds to collagen by introducing functional groups onto the collagen using P-chi-collagen matrix complex and induces homogenous nucleation. CMC stabilizes dentine matrix protein 1 (DMP1) in ACP to form nanocomplexes of CMC/ACP, which can be made into scaffolds. The nanoclusters formed can infiltrate into gap zones of collagen leading to intrafibrillar mineralization. It has been proved to follow biomimetic strategy, thus aiding in biomineralization of dentin.

5.5 Polydopamine [45]

It is a synthetic mimic of marine adhesive protein consisting of 3, 4-dihydroxy-L-phenylalanine which helps in providing new nucleation site for HAp and binds to collagen fiber. This can adhere to almost all substrates and has good stability in many environments. It has surface-anchored catecholamine moieties which binds to calcium ions, enabling the formation of HA crystals along c-axes. It also can cause tubular occlusion due to densely packed HA crystals. Hence, it can be used as dentin remineralizing agent as well as therapeutic agent for dentin hypersensitivity.

5.6 Polyamidoamine Dendrimer (PAMAM) [46,47]

It binds to collagen fibrils by recruiting ACP nano-precursors into collagen matrix. It guides mesocrystals to assemble into large ones and also induces the periodicity of the mineralized fibrils. It promotes biomimetic intrafibrillar mineralization of dentin by following structural hierarchy. It can cause sequestration of the mineral ions and can act as template for nucleation, proving it to be a potent remineralizing material.

5.7 Remineralizing Mediums

Several remineralizing mediums such as Portland cement, calcium phosphate remineralizing solution, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), artificial saliva, bioactive glass, calcium chloride solution, and metastable calcium phosphate solution, simulated body fluid (SBF), phosphate-containing solution or gel and phosphate-buffered saline (PBS) have been tried as mineralization medium [48].

6. RECENT STUDIES ON DENTIN BIOMIMETIC REMINERALIZATION

Gower et al pioneered a process of polymer-induced liquid-precursor (PILP) [PILP] method which relies on the presence of process directing agents that stabilize saturated calcium phosphate solutions by forming nano droplets rich in these ions. On contact with collagen fibrils, nano droplets release ions into collagen fibrils and promote formation of amorphous calcium phosphate which gradually turns into oriented apatite crystals similar to dentin. A number of process-directing systems have been identified and have been tested on collagen or on demineralized dentin. [49]

Currently available biomimetic systems for dentin biomimetic remineralization of hybrid layer and affected dentin:reas follows:

- Resin doped with Carboxy Methyl Chitosan and calcium phosphate microfillers: The CMC-CAP containing resins could induce the biomimetic remineralization of caries affected dentin and improves the bonding durability by rapid and complete intrafibrillar crystallization. The excellent ability of CMC in stabilizing mineralization precursors and directing biomimetic mineralization was demonstrated with the mineral precursors showing dynamic infiltration into collagen fibrils. It also demonstrates higher resin dentin bond strength. [50]
- PAMAM and rechargeable composite containing nanoparticles of amorphous calcium phosphate: This strategy achieved complete dentin remineralization by restoring the pre-demineralized dentin hardness to that of healthy dentin with prolonged fluid challenges. This could be attributed to the superior nucleation templates Ca and P ion recharge and re-release, and acid neutralization [51].
- On cross-linking of dentin with *glutaraldehyde*, collagen could promote dentin biomimetic remineralization, resulting in an improved mechanical properties and bio stability. The aldehyde group has dual function of collagen cross-linking and calcium binding. It not only binds with the specific amino residues of the collagen molecule, but also provides additional nucleation sites for calcium phosphate crystals.[52]
- Several *in-vitro* studies are evidenced in literature on materials such as modification of *self-etch adhesive with carrier loaded with polyaspartic acid Si-ACP particles* [53], use of experimental primers containing biomimetic analogues and adhesives with ion-releasing components such as *polydopamine, CPP-ACP, BAG, CaSi, ZnO, and CaP* to achieve biomimetic remineralization. It shows the possibility to promote mineral precipitation within the hybrid layer and reduce collagen degradation [54].

7. CONCLUSION

In future, restorative dentistry would no longer be using inert materials that simply fill the space left

by cavity preparation, but instead, should stimulate dental tissues regeneration and/or by themselves self-mending. Evidence for the most biomimetic approaches for enamel and dentin remineralization is still in their laboratory stage. Clinical translation of this biomimetic research can be considered as the boon to restorative dentistry. New mechanisms for adhesion, integration, and sealing of dentin using biomimetic technologies can emerge as a major turnover in restorative field.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Blok V, Gremmen B. Ecological innovation: Biomimicry as a new way of thinking and acting ecologically. Journal of Agricultural and Environmental Ethics. 2016;29(2): 203-17.
2. Sonarkar S, Purba R. Bioactive materials in conservative dentistry. Int J Contemp Dent Med Rev. 2015;2015:1-4.
3. Goldberg M, Lacerda-Pinheiro S, Jegat N, Six N, Septier D, Priam F, Bonnefoix M, Tompkins K, Chardin H, Denbesten P, Veis A. The impact of bioactive molecules to stimulate tooth repair and regeneration as part of restorative dentistry. Dental Clinics. 2006;50(2):277-98.
4. Liu Y, Tjäderhane L, Breschi LO, Mazzoni A, Li N, Mao J, Pashley DH, Tay FR. Limitations in bonding to dentin and experimental strategies to prevent bond degradation. Journal of Dental Research. 201;90:953-68.
5. Guentsch A, Busch S, Seidler K, Kraft U, Nietzsche S, Preshaw PM, Chromik JN, Glockmann E, Jandt KD, Sigusch BW. Biomimetic mineralization: Effects on human enamel *in vivo*. Advanced Engineering Materials. 2010;12:B571-6.
6. Janet Moradian-Oldak. Protein- mediated enamel mineralization. Front Biosci. 2013; 17:1996–2023
7. Najeeb S, Khurshid Z, Zafar MS, Khan AS, Zohaib S, Martí JM, Sauro S, Matinlinna JP, Rehman IU. Modifications in glass ionomer cements: Nano-sized fillers and bioactive nanoceramics. International Journal of Molecular Sciences. 2016; 17(7):1134.
8. Eggert FM, Allen GA, Burgess RC. Amelogenins. Purification and partial characterization of proteins from developing bovine dental enamel. Biochemical Journal. 1973;131(3):471-84.
9. Pandya M, Lin T, Li L, Allen MJ, Jin T, Luan X, Diekwisch TG. Posttranslational amelogenin processing and changes in matrix assembly during enamel development. Frontiers in Physiology. 2017;8:790-795.
10. Braga RR, Habelitz S. Current Developments on Enamel and Dentin Remineralization. Current Oral Health Reports. 2019;6:257-63.
11. Pandya M, Diekwisch TG. Enamel biomimetics—fiction or future of dentistry. International Journal of Oral Science. 2019;11:1-9.
12. Cai Y, Tang R. Calcium phosphate nanoparticles in biomineralization and biomaterials. Journal of Materials Chemistry. 2008;18(32):3775-87.
13. Ruan Q, Moradian-Oldak J. Amelogenin and enamel biomimetics. Journal of Materials Chemistry B. 2015;3(16):3112-29.
14. Yang X, Wang L, Qin Y, Sun Z, Henneman ZJ, Moradian-Oldak J, Nancollas GH. How amelogenin orchestrates the organization of hierarchical elongated microstructures of apatite. The Journal of Physical Chemistry B. 2010;114(6):2293-300.
15. Iijima M, Moradian-Oldak J. Control of apatite crystal growth in a fluoride containing amelogenin-rich matrix. Biomaterials. 2005;26(13):1595-603.
16. Cao Y, Mei ML, Li QL, Lo EC, Chu CH. Enamel prism-like tissue regeneration using enamel matrix derivative. Journal of Dentistry. 2014;42(12):1535-42.
17. Wu D, Yang J, Li J, Chen L, Tang B, Chen X, Wu W, Li J. Hydroxyapatite-anchored dendrimer for in situ remineralization of human tooth enamel. Biomaterials. 2013; 34:036–5047.

18. Chen M, Yang J, Li J, Liang K, He L, Lin Z, Chen X, Ren X, Li J. Modulated regeneration of acid-etched human tooth enamel by a functionalized dendrimer that is an analog of amelogenin. Acta Biomater. 2014;10:4437–4446.
19. Chung HY, Li CC, Hsu CC. Characterization of the effects of 3DSS peptide on remineralized enamel in artificial saliva. J. Mech. Behav. Biomed. Mater. 2012;6:74–79.
20. Chung HY, Li CC. Microstructure and nano mechanical properties of enamel remineralize with asparagine-serine-serine peptide. Mate. Sci. Eng. C. Mater. Biol. Appl. 2013;33:969–973.
21. Li L, Mao C, Wang J, Xu X, Pan H, Deng Y, Gu X, Tang R. Bio-inspired enamel repair via Glu-directed assembly of apatite nanoparticles: An approach to biomaterials with optimal characteristics. Adv. Mater. 2011;23:4695–47.
22. Milly H, Festy F, Watson TF, Thompson I, Banerjee A. Enamel white spot lesions can remineralise using bio-active glass and polyacrylic acid-modified bio-active glass powders. J. Dent. 2014;42:158–166.
23. Zhang X, Li Y, Sun X, Kishen A, Deng X, Yang X, Wang H, Cong C, Wang Y, Wu M. Biomimetic remineralization of demineralized enamel with nano-complexes of phosphorylated chitosan and amorphous calcium phosphate. J. Mater. Sci. Mater. Med. 2014;25:2619–2628.
24. Reynolds EC. Remineralization of enamel subsurface lesions by casein phosphopeptide-stabilized calcium phosphate solutions. J. Dent. Res. 1997; 76:1587–1595.
25. Fletcher J, Walsh D, Fowler CE, Mann S. Electrospun mats of PVP/ACP nanofibres for remineralization of enamel tooth surfaces. Cryst Eng Comm. 2011;13(11): 3692-7.
26. Huang SB, Gao SS, Yu HY. Effect of nano-hydroxyapatite concentration on remineralization of initial enamel lesion *in vitro*. Biomedical Materials. 2009;4(3): 034104.
27. Brunton PA, Davies RP, Burke JL, Smith A, Aggeli A, Brookes SJ, Kirkham J. Treatment of early caries lesions using biomimetic self-assembling peptides–a clinical safety trial. British Dental Journal. 2013;215(4):E6-.
28. Li QL, Ning TY, Cao Y, Zhang WB, Mei ML, Chu CH. A novel self-assembled oligopeptide amphiphile for biomimetic mineralization of enamel. BMC Biotechnology. 2014;14(1):1-12.
29. Hsu CC, Chung HY, Yang JM, Shi W, Wu B. Influence of 8DSS peptide on nano-mechanical behaviour of human enamel. J. Dent. Res. 2011;90:88–92.
30. Cao Y, Mei ML, Li QL, Lo EC, Chu CH. Agarose hydrogel biomimetic mineralization model for the regeneration of enamel prismlike tissue. ACS Appl. Mater. Interfaces. 2014;6:410–420.
31. Ruan Q, Liberman D, Bapat R, Chandrababu KB, Phark JH, Moradian-Oldak J. Efficacy of amelogenin-chitosan hydrogel in biomimetic repair of human enamel in pH-cycling systems. Journal of Biomedical Engineering and Informatics. 2016;2(1):119.
32. Kwak SY, Litman A, Margolis HC, Yamakoshi Y, Simmer JP. Biomimetic enamel regeneration mediated by leucine-rich amelogenin peptide. Journal of Dental Research. 2017;96(5):524-30.
33. Zaharia A, Muşat V, Anghel EM, Atkinson I, Mocioiu OC, Buşilă M, Pleşcan VG. Biomimetic chitosan-hydroxyapatite hybrid biocoatings for enamel remineralization. Ceramics International. 2017;43(14): 11390-402.
34. Wang H, Xiao Z, Yang J, Lu D, Kishen A, Li Y, Chen Z, Que K, Zhang Q, Deng X, Yang X. Oriented and ordered biomimetic remineralization of the surface of demineralized dental enamel using HAP@ ACP nanoparticles guided by glycine. Scientific Reports. 2017;7(1):1-3.
35. Xiao Z, Que K, Wang H, An R, Chen Z, Qiu Z, Lin M, Song J, Yang J, Lu D, Shen M. Rapid biomimetic remineralization of the demineralized enamel surface using nano-particles of amorphous calcium phosphate guided by chimaeric peptides. Dental Materials. 2017;33(11):1217-28.
36. Xie RQ, Feng ZD Li SW, Xu BB. EDTA-assisted self-assembly of fluoride-substituted hydroxyapatite coating on enamel substrate. Cryst. Growth. Des. 2011;11:5206–5214.
37. Kinney JH, Habelitz, S. Marshall, SJ. Marshall, G.W. The importance of intrafibrillar mineralization of collagen on the mechanical properties of dentin. J. Dent. Res. 2003;82:957–961

38. Burwell AK, Thula-Mata T, Gower LB, Habelitz S, Kurylo M, HoSP, et al. Functional remineralization of dentin lesions using polymer-induced liquid-precursor process. PLoS One. 2012;7(6): e38852.
39. Ten Cate JM, Buzalaf MAR. Fluoride mode of action: Once there was an observant dentist. J Dent Res. 2019;98(7):725–30.
40. Liu Y, Mai S, Li N, Yiu CK, Mao J, Pashley DH, et al. Differences between top-down and bottom-up approaches in mineralizing thick, partially demineralized collagen scaffolds. Acta Biomaterialia. 2011;7: 1742–51.
41. Qi YP, Li N, Niu LN, Primus CM, Ling JQ, Pashley DH, Tay FR. Remineralization of artificial dentinal caries lesions by biomimetically modified mineral trioxide aggregate. Acta Biomater. 2012;8:36–842.
42. Tay FR, Pashley DH. Guided tissue remineralisation of partially demineralised human dentine. Biomaterials. 2008;29: 1127–1137.
43. Gu LS, Kim YK, Liu Y, Takahashi K, Arun S, Wimmer CE, Osorio R, Ling JQ, Looney SW, Pashley DH, et al. Immobilization of a phosphonated analog of matrix phosphoproteins within cross-linked collagen as a templating mechanism for biomimeticmineralization. Acta Biomater. 2011;7:268–277.
44. Xu Z, Neoh KG, Lin CC, Kishen A. Biomimetic deposition of calcium phosphate minerals on the surface of partially demineralized dentine modified with phosphorylated chitosan. J. Biomed. Mater. Res. B Appl. Biomater. 2011;98: 150–159.
45. Zhou YZ, Cao Y, Liu W, Chu CH, Li QL. Polydopamine-induced tooth remineralization. ACS Appl. Mater. Interfaces. 2012;4:6901–6915.
46. Li J, Yang J, Li J, Chen L, Liang K, Wu W, Chen X, Li J. Bioinspired intrafibrillar mineralization of human dentine by PAMAM dendrimer. Biomaterials. 2013;34: 6738–6747.
47. Zhou Y, Yang J, Lin Z, Li J, Liang K, Yuan H, Li S, Li J. Triclosan-loaded poly (amidoamine) dendrimer for simultaneous treatment and remineralization of human dentine. Colloids Surf. B Biointerfaces. 2014;115:237–243.
48. Jee SS, Thula TT, Gower LB. Development of bone-like composites via the polymer-induced liquid-precursor (PILP) process. Part 1: Influence of polymer molecular weight. Acta Biomater. 2010;6:3676–3686.
49. Niu LN, Zhang W, Pashley DH, Breschi L, Mao J, Chen JH, Tay FR. Biomimetic remineralization of dentin. Dental materials. 2014;30(1):77-96.
50. Huang Z, Qi Y, Zhang K, Gu L, Guo J, Wang R, Mai S. Use of experimental-resin-based materials doped with carboxymethyl chitosan and calcium phosphate microfillers to induce biomimetic remineralization of caries-affected dentin. Journal of the Mechanical Behavior of Biomedical Materials. 2019;89:81-8.
51. Liang K, Xiao S, Wu J, Li J, Weir MD, Cheng L, Reynolds MA, Zhou X, Xu HH. Long-term dentin remineralization by poly (amido amine) and rechargeable calcium phosphate nanocomposite after fluid challenges. Dental Materials. 2018;34(4): 607-18.
52. Xu Z, Neoh KG, Lin CC, Kishen A. Biomimetic deposition of calcium phosphate minerals on the surface of partially demineralized dentine modified with phosphorylated chitosan. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2011;98(1):150-9.
53. Wu Z, Wang X, Wang Z, Shao C, Jin X, Zhang L, Pan H, Tang R, Fu B. Self-etch adhesive as a carrier for ACP Nanoprecursors to deliver biomimetic remineralization. ACS Applied Materials & Interfaces. 2017;9(21):17710-7.
54. Braga RR, Fronza BM. The use of bioactive particles and biomimetic analogues for increasing the longevity of resin-dentin interfaces: A literature review. Dental Materials Journal. 2020;39(1):62-8.

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