[DOI]10.12016/j.issn.2096-1456.2021.09.010

·综述·

# 纳米磷酸钙盐改性牙科材料防治牙体牙髓病研究进展

黄彦楠，　程磊
口腔疾病研究国家重点实验室　国家口腔疾病临床医学研究中心　四川大学华西口腔医院牙体牙髓病科，四川　成都(610041)

【摘要】　纳米材料通常是指直径1～100 nm的微小颗粒，往往具有独特的物理化学性质，是牙科生物材料发展的主要方向之一。纳米磷酸钙盐改性牙科材料在窝沟封闭、牙体树脂修复、牙体粘接、根管封闭等方面有广泛的应用。目前研究表明，纳米磷酸钙盐改性后的牙科材料具有更强的机械性能，还显示出钙磷离子长期释放和较好的离子再充能力，能够有效促进牙体硬组织再矿化，具有良好的应用前景。但目前研究难以准确模拟口腔内的复杂环境，因此，纳米磷酸钙盐改性牙科材料的生物相容性、细胞毒性及在临床运用的效果等仍需进一步验证。本文就近年来纳米磷酸钙盐改性牙科材料在牙体牙髓疾病防治方面研究的进展进行综述。

【关键词】　纳米磷酸钙盐；　牙科材料；　材料改性；　窝沟封闭剂；　复合树脂；　树脂粘接剂；　根管封闭剂；　龋病；　牙髓病；　口腔微生物
【中图分类号】　R78　【文献标志码】　A　【文章编号】　2096-1456(2021)09-0634-04
开放科学(资源服务)标识码(OSID)
【引用著录格式】　黄彦楠, 程磊. 纳米磷酸钙盐改性牙科材料防治牙体牙髓病研究进展[J]. 口腔疾病防治, 2021, 29(9): 634-637. doi: 10.12016/j.issn.2096-1456.2021.09.010.

**Research progress on nano-calcium phosphate modified dental materials for the prevention and treatment of dental pulp diseases**

HUANG Yannan, CHENG Lei. State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Department. of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
Corresponding author: CHENG Lei, Email: chengleidentist@163.com, Tel: 86-28-85501439

【Abstract】　Nanomaterials usually refer to tiny particles with a diameter of 1-100 nm, which often have unique physicochemical properties and are one of the main areas of research interest for development of dental biomaterials. Nano-calcium phosphate modified dental materials have been widely used in pit and fissure sealing, dental resin restoration, tooth adhesion, and root canal sealing. The current research shows that the dental material modified by nano-calcium phosphate has stronger mechanical properties and shows long-term calcium and phosphorus ion release and excellent ion recharging ability, which can promote the remineralization of tooth hard tissue and has good prospects for application. However, it is difficult to accurately simulate the complex environment of the oral cavity. Therefore, the biocompatibility, cytotoxicity and effect of clinical application of nano-calcium phosphate modified dental materials still needs further study. This review summarizes and discusses the recent research progress regarding nano-calcium phosphate modified dental materials in the prevention and treatment of dental pulp diseases.

【Key words】　nanometer calcium phosphate;　dental materials;　material modification;　pit-and-fissure sealant;　composite resin;　resin adhesive;　root canal sealant;　dental decay;　dental pulp disease;　oral microorganisms
**J Prev Treat Stomatol Dis, 2021, 29(9): 634-637.**
【Competing interests】　The authors declare no competing interests.
This study was supported by the grants from National Natural Science Foundation of China (No. 81870759).

【收稿日期】2020-11-04；　【修回日期】2021-01-24
【基金项目】国家自然科学基金项目(81870759)
【作者简介】黄彦楠，医师，硕士研究生，Email：susynan@163.com
【通信作者】程磊，教授，博士，Email：chengleidentist@163.com，Tel：86-28-85501439

纳米磷酸钙盐改性牙科材料直径通常在1～100 nm之间，其大比表面积和高电荷密度使其能更大程度地与细菌细胞负电荷表面相互作用，增强抗菌活性，在抗菌治疗中具有广阔的应用前景[1-2]，是目前牙科生物材料发展的主要方向之一。本文就近年来纳米磷酸钙盐改性牙科材料防治牙体牙髓疾病的研究进展进行综述。

## 1　纳米磷酸钙改性窝沟封闭剂

窝沟封闭是预防磨牙窝沟龋的最有效方法。最常应用的窝沟封闭剂主要是树脂型窝沟封闭剂和玻璃离子型窝沟封闭剂。树脂型窝沟封闭剂具有较好的机械性能，但固化时容易发生聚合收缩。高微渗漏率容易产生边缘继发龋，最终导致修复失败[3]。玻璃离子型窝沟封闭剂能够释放氟离子和再充氟，具备促再矿化能力，但其脆性大、易折断。因此，目前窝沟封闭剂材料的研究重点在于保留材料的原有优良性能的同时，减少边缘微渗漏发生、增强抗菌性和再矿化能力和提高机械性能。

Ibrahim等[4]添加不同浓度的无定形磷酸钙纳米颗粒（nanoparticles of amorphous calcium phosphate，NACP）对含有二甲基氨基十六烷基甲基丙烯酸酯（dimethylaminohexadecyl methacrylate，DMAHDM）的窝沟封闭剂进行改性，最终确定NACP质量分数为20%的窝沟封闭剂显示出理想的机械性能、理想的流动和处理性能，以及长期钙磷离子释放和较好的离子再充能力。另外，该课题组又在pH循环模型中进一步评价了NACP改性窝沟封闭剂的防龋效果[5]。这种新型的封闭剂为临床上预防窝沟龋提供了一个可行的策略[4-5]。

## 2　纳米磷酸钙改性复合树脂材料

复合树脂材料是目前临床上应用最广泛的龋病治疗充填修复材料[6]。然而，相比于牙釉质和其他牙齿修复材料，复合树脂表面更容易聚集微生物形成生物膜，进而产生继发龋[7]。树脂充填修复治疗失败的两大原因是继发龋形成和充填体折裂[6]。目前对复合树脂改良的方法之一就是在树脂填料中加入具有促矿化作用的材料，促进牙体硬组织再矿化，一定程度上抑制继发龋形成。这种填料主要是粒径为1～55 μm的无定形磷酸钙（amorphous calcium phosphate，ACP），能够释放钙、磷离子形成羟基磷灰石。然而，传统磷酸钙改性的复合树脂中材料机械性能不理想，处于应力集中部位或承受咬合力过大时容易折裂、脱落[8]。Xu等[9]等首次通过喷雾干燥技术合成了纳米级无水磷酸二钙，将其作为填料和碳化硅晶须加入复合树脂，之后，Xu等[10]利用相同的技术合成了NACP，并研究了NACP填料水平和环境pH值对复合材料力学性能和离子释放的影响。结果显示，相比传统的ACP复合树脂，NACP复合树脂的强度和离子释放水平大大提高，提示了NACP材料的优势。Moreau等[11]还发现这种NACP复合材料能适度抑制变异链球菌的生长，但其抗菌性能和机制还需进一步研究。Cheng等[12]在此基础上对NACP复合材料进行改性，添加了纳米银、季铵盐、氯己定等不同的抗菌剂，进一步增强其抗菌性能。体外实验结果表明改性后的复合树脂能够调节口腔微生态平衡，抑制唾液生物膜代谢和产酸，在临床防治龋病方面具有良好的应用前景。为了更接近真实口腔微环境，Melo等[13]首次开展了人体内试验，发现与普通填料复合物相比，NACP复合材料显著抑制了龋的形成。

修复失败的另一个常见原因是修复体折裂。为了克服这一问题，Wu等[14]研发了含有DMAHDM和含双环戊二烯（dicyclopentadiene，DCPD）的聚脲甲醛外壳微胶囊的复合材料，以恢复修复体裂开后的承重能力。当修复体裂纹生成使微胶囊随之破裂，释放DCPD进入裂纹面，自主修复裂缝。并且，Wu等[15]还添加了NACP，赋予材料促进牙体硬组织再矿化的性能，进一步增强修复效果。

随着人口老龄化，根面龋的发病率不断上升[16]。对根面龋进行修复时，其龈下部分往往难以清洁，修复材料不具备抗菌性能，使得修复易失败。Xiao等[17]在复合材料中添加纳米银、2-甲基丙烯酰氧乙基磷酰胆碱、DMAHDM等抗菌剂，用于抑制根面致龋微生物，同时构建了牙龈卟啉单胞菌、放线共生放线杆菌和具核梭杆菌三菌种生物膜模型测试其抗菌性能。实验结果提示这种新型材料能够显著抑制三菌种生物膜代谢产糖。并且，Xiao等[17]还在复合材料中添加了NACP赋予其促进再矿化的性能，一定程度上弥补老年人唾液流量减少、唾液缓冲和促进再矿化能力下降的影响。变异链球菌、嗜酸乳杆菌是老年人根面龋中的主要微生物[18]。此外，白色念珠菌也是老年人根面龋中的常见检出微生物[19]。Zhou等[20]合成的含有DMAHDM的NACP复合材料具有良好的抗菌

性能，能够抑制变异链球菌、嗜酸乳杆菌和白色念珠菌的生长代谢，且释放钙、磷离子，促进再矿化，有效保护根面牙本质。

## 3　纳米磷酸钙改性树脂粘接剂

充填修复材料和牙体之间的树脂粘接界面在口腔环境的长期作用下，容易产生微渗漏，同时牙本质小管内也可能存在残留的微生物，从而导致继发龋。因此，在不影响粘接性能的前提下，赋予粘接剂再矿化性能，降低因微渗漏造成继发龋的风险是一个预防继发龋、提高修复体使用寿命的可行方法。

Melo等[21]首次将纳米银粒子（NAg）和NACP加入粘接剂中，研究其牙本质粘接强度和对牙菌斑生物膜的影响。结果显示加入NAg和NACP不降低粘接强度。大量NACP浸润牙本质小管，改性后的粘接剂显著降低牙菌斑生物膜的活性和产酸能力。Chen等[22]将二甲基氨基十二烷基甲基丙烯酸酯（dimethylaminododecyl methacrylate，DMADDM）和NACP加入树脂粘接剂，在pH = 4的时候钙磷离子显著释放，能够抑制生物膜、促进再矿化。相比于过去使用的ACP，添加NACP的树脂粘接剂机械强度提高，且具有良好的流动性能够渗入牙本质小管内。Li等[23-24]对加入DMAHDM及NACP的牙本质粘接剂进行6个月水老化实验验证了其粘接性能，并且加入磁性纳米材料进一步增强粘接剂渗透性，加强树脂-牙体结合，抑制修复边缘的继发龋。

添加NACP树脂粘接剂的另一优势是可通过漱口水等溶液反复充入钙磷离子，具有长期再矿化效果。Al-Qarni等[25]研制一种含NACP和2-甲基丙烯酰氧乙基磷酰胆碱（2-methacryloyloxy ethyl phosphorylcholine，MPC）纳米颗粒的粘接树脂，并首次研究了加入MPC对离子再充和再释放的影响。用唾液生物膜进行抗菌测试，该新型粘接剂可显著降低蛋白质吸附、生物膜生长和乳酸含量，同时保有优良的钙磷子释放、离子再充能力和牙本质结合强度。

在粘接剂中添加NACP，可促进牙体硬组织再矿化，弥补微渗漏产生的不利影响[26-27]。

## 4　纳米磷酸钙改性根管封闭剂

根管治疗是治疗牙髓根尖周病的首选方法，在根管冲洗的同时，使用具有抗菌性能的根管封闭剂，可以有效消除根管内残留的微生物并杀死新的入侵病原体。但是，有研究报道在根管预备过程中使用的次氯酸钠、乙二胺四乙酸等冲洗剂对构成牙本质主要结构的钙、磷离子的影响，会使牙本质结构损伤和硬度下降[28]。为了解决这一问题，Wang等[29]首次研制了一种新型的生物活性根管封闭剂，该根管封闭剂中加入了NACP，能释放钙、磷离子，且与根管牙本质壁有良好的结合。同时，该根管封闭剂内还加入了DMAHDM、MPC，能有效抑制多菌种根管内生物膜（内氏放线菌、具核梭杆菌、粪肠球菌）感染。此外，其他学者在研究抗菌改性根管封闭剂时，也会同时添加不同质量分数的NACP和抗菌成分，合成具有多重功效的新型根管封闭剂[30-31]。

## 5　小　结

纳米磷酸钙盐改性牙科材料相比于传统磷酸钙盐牙科材料的力学性能有较大优势，且还具有离子再充特性。然而，目前已有的研究大多是在体外进行的，纳米磷酸钙盐改性牙科材料在体内防治牙体牙髓疾病的效果、生物相容性、细胞毒性等仍需进一步研究。

**【Author contributions】** Huang YN collected the references and wrote the article. Cheng L revised the article. All authors read and approved the final manuscript as submitted.

### 参考文献

[1] Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions[J]. Nat Rev Microbiol, 2018, 16(12): 745-759. doi: 10.1038/s41579-018-0089-x.

[2] Fornaguera C, Solans C. Characterization of polymeric nanoparticle dispersions for biomedical applications: size, surface charge and stability[J]. Pharm Nanotechnol, 2018, 6(3): 147-164. doi: 10.2174/2211738506666180706121515.

[3] Fiorati-Aguiar SM, Lucisano MP, Silva L, et al. Mechanical, chemical and antimicrobial properties of a bisphenol A-free pit-and-fissure sealant[J]. Ame J Dent, 2018, 31(6): 279-284.

[4] Ibrahim MS, Alqarni FD, Al-Dulaijan YA, et al. Tuning nano-amorphous calcium phosphate content in novel rechargeable antibacterial dental sealant[J]. Materials (Basel), 2018, 11(9): 1544. doi: 10.3390/ma11091544.

[5] Ibrahim MS, Balhaddad AA, Garcia IM, et al. pH-responsive calcium and phosphate-ion releasing antibacterial sealants on carious enamel lesions *in vitro*[J]. J Dent, 2020, 97: 103323. doi: 10.1016/j.jdent.2020.103323.

[6] Eltahlah D, Lynch CD, Chadwick BL, et al. An update on the reasons for placement and replacement of direct restorations[J]. J Dent, 2018, 72: 1-7. doi: 10.1016/j.jdent.2018.03.001.

[7] Hao Y, Huang XY, Zhou XE, et al. Influence of dental prosthesis and restorative materials interface on oral biofilms[J]. Int J Mol Sci, 2018, 19(10): 3157. doi: 10.3390/ijms19103157.

[8] Braga RR. Calcium phosphates as ion-releasing fillers in restorative resin-based materials[J]. Dent Mater, 2019, 35(1): 3-14. doi: 10.1016/j.dental.2018.08.288.

[9] Xu HH, Sun L, Weir MD, et al. Nano DCPA-whisker composites with high strength and Ca and PO(4) release[J]. J Dent Res, 2006, 85(8): 722-727. doi: 10.1177/154405910608500807.

[10] Xu HH, Moreau JL, Sun L, et al. Nanocomposite containing amorphous calcium phosphate nanoparticles for caries inhibition[J]. Dent Mater, 2011, 27(8): 762-769. doi: 10.1016/j.dental.2011.03.016.

[11] Moreau JL, Sun L, Chow LC, et al. Mechanical and acid neutralizing properties and bacteria inhibition of amorphous calcium phosphate dental nanocomposite[J]. J Biomed Mater Res B Appl Biomater, 2011, 98(1): 80-88. doi: 10.1002/jbm.b.31834.

[12] Cheng L, Zhang K, Zhou CC, et al. One-year water-ageing of calcium phosphate composite containing nano-silver and quaternary ammonium to inhibit biofilms[J]. Int J Oral Sci, 2016, 8(3): 172-181. doi: 10.1038/ijos.2016.13.

[13] Melo MA, Weir MD, Rodrigues LK, et al. Novel calcium phosphate nanocomposite with caries-inhibition in a human in situ model[J]. Dent Mater, 2013, 29(2): 231-240. doi: 10.1016/j.dental.2012.10.010.

[14] Wu J, Weir MD, Melo MA, et al. Development of novel self-healing and antibacterial dental composite containing calcium phosphate nanoparticles[J]. J Dent, 2015, 43(3): 317-326. doi: 10.1016/j.jdent.2015.01.009.

[15] Wu J, Zhou H, Weir MD, et al. Effect of dimethylaminohexadecyl methacrylate mass fraction on fracture toughness and antibacterial properties of CaP nanocomposite[J]. J Dent, 2015, 43(12): 1539-1546. doi: 10.1016/j.jdent.2015.09.004.

[16] Grippo JO, Coleman TA, Messina AM, et al. A literature review and hypothesis for the etiologies of cervical and root caries[J]. J Esthet Restor Dent, 2018, 30(3): 187-192. doi: 10.1111/jerd.12365.

[17] Xiao S, Wang H, Liang K, et al. Novel multifunctional nanocomposite for root caries restorations to inhibit periodontitis-related pathogens[J]. J Dent, 2019, 81: 17-26. doi: 10.1016/j.jdent. 2018.12.001.

[18] Hellyer P. Root caries: from prevalence to therapy[J]. BDJ, 2018, 224: 765. doi: 10.1038/sj.bdj.2018.412.

[19] Pereira D, Seneviratne CJ, Koga-Ito CY, et al. Is the oral fungal pathogen *Candida albicans* a cariogen?[J]. Oral Dis, 2018, 24(4): 518-526. doi: 10.1111/odi.12691.

[20] Zhou W, Zhou X, Huang X, et al. Antibacterial and remineralizing nanocomposite inhibit root caries biofilms and protect root dentin hardness at the margins[J]. J Dent, 2020, 97: 103344. doi: 10.1016/j.jdent.2020.103344.

[21] Melo MA, Cheng L, Zhang K, et al. Novel dental adhesives containing nanoparticles of silver and amorphous calcium phosphate [J]. Dent Mater, 2013, 29(2): 199-210. doi: 10.1016/j.dental.2012.10.005.

[22] Chen C, Weir MD, Cheng L, et al. Antibacterial activity and ion release of bonding agent containing amorphous calcium phosphate nanoparticles[J]. Dent Mater, 2014, 30(8): 891-901. doi: 10.1016/j.dental.2014.05.025.

[23] Li Y, Hu X, Ruan J, et al. Bonding durability, antibacterial activity and biofilm pH of novel adhesive containing antibacterial monomer and nanoparticles of amorphous calcium phosphate[J]. J Dent, 2019, 81: 91-101. doi: 10.1016/j.jdent.2018.12.013.

[24] Li Y, Hu X, Xia Y, et al. Novel magnetic nanoparticle-containing adhesive with greater dentin bond strength and antibacterial and remineralizing capabilities[J]. Dent Mater, 2018, 34(9): 1310-1322. doi: 10.1016/j.dental.2018.06.001.

[25] Al-Qarni FD, Tay F, Weir MD, et al. Protein-repelling adhesive resin containing calcium phosphate nanoparticles with repeated ion-recharge and re-releases[J]. J Dent, 2018, 78: 91-99. doi: 10.1016/j.jdent.2018.08.011.

[26] Yue S, Wu J, Zhang Q, et al. Novel dental adhesive resin with crack self-healing, antimicrobial and remineralization properties [J]. J Dent, 2018, 75: 48-57. doi: 10.1016/j.jdent.2018.05.009.

[27] Wu J, Zhou C, Ruan J, et al. Self-healing adhesive with antibacterial activity in water-aging for 12 months[J]. Dent Mater, 2019, 35 (8): 1104-1116. doi: 10.1016/j.dental.2019.05.004.

[28] Saha SG, Sharma V, Bharadwaj A, et al. Effectiveness of various endodontic irrigants on the micro-hardness of the root canal dentin: an *in vitro* study[J]. J Clin DiagnRes, 2017, 11(4): ZC01-ZC04. doi: 10.7860/jcdr/2017/24018.9472.

[29] Wang L, Xie X, Li C, et al. Novel bioactive root canal sealer to inhibit endodontic multispecies biofilms with remineralizing calcium phosphate ions[J]. J Dent, 2017, 60: 25-35. doi: 10.1016/j.jdent.2017.02.011.

[30] Baras BH, Sun J, Melo M, et al. Novel root canal sealer with dimethylaminohexadecyl methacrylate, nano-silver and nano-calcium phosphate to kill bacteria inside root dentin and increase dentin hardness[J]. Dent Mater, 2019, 35(10): 1479-1489. doi: 10.1016/j.dental.2019.07.014.

[31] Baras BH, Wang S, Melo M, et al. Novel bioactive root canal sealer with antibiofilm and remineralization properties[J]. J Dent, 2019, 83: 67-76. doi: 10.1016/j.jdent.2019.02.006.

（编辑　张琳）