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纳米粒子在正畸釉质脱矿预防中的应用

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【摘要】 牙釉质脱矿是正畸治疗最常见的不良反应之一。正畸矫治器影响口腔清洁能力，易导致菌斑堆积及口腔菌群失调，致龋菌产酸引起牙釉质脱矿，不仅影响美观，还可能危害口腔健康，是一个亟待解决的难题。纳米粒子(nanoparticles，NPs)通常指直径为1～100 nm的固体颗粒，理化性质独特，能为正畸釉质脱矿预防提供新策略。回顾相关文献，用于预防正畸釉质脱矿的NPs按其功能可分为抗菌、再矿化及载体型三类。应用NPs改性正畸粘接剂赋予其抗菌或再矿化性能的研究最多；也有研究利用NPs对正畸矫治器进行表面涂层或整体掺杂改性使其具备抗菌性能。上述两种方式的优势在于不依赖患者的依从性。此外，NPs改性的氟保护漆及负载抗菌或再矿化制剂的纳米载体可用于促进正畸患者的口腔保健，该途径能发挥持续预防作用，但依赖患者配合。研究显示，NPs的小尺寸效应可增强其性能，但可能存在一定安全性问题，且仍对改性后材料本身理化性能有一定的影响，这些问题还需进一步探索。虽然现有研究还存在一定局限性，但可预见，未来纳米粒子在正畸釉质脱矿的预防中有望发挥重要作用。

【关键词】 纳米粒子； 纳米载体； 口腔正畸； 牙釉质脱矿； 白垩斑； 粘接剂； 矫治器； 口腔保健； 抗菌； 再矿化

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Application of nanoparticles in preventing enamel demineralization during orthodontics

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【Abstract】 Enamel demineralization is one of the most common adverse reactions to orthodontic treatment. The existence of orthodontic appliances affects oral hygiene maintenance, which easily leads to plaque accumulation and oral flora dysbiosis, and cariogenic bacteria produce acid to cause enamel demineralization. It not only affects aesthetics but may develop into caries and endanger oral health. Therefore, enamel demineralization has become an urgent problem. Nanoparticles generally refer to solid particles with diameters of 1 to 100 nm and have unique physicochemical proper-

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ties that provide a new strategy for preventing enamel demineralization during orthodontics. Reviewing the relevant literature, nanoparticles used for the prevention of enamel demineralization in orthodontics may be classified into antibacterial, remineralization and carrier-type nanoparticles according to their functions. Most research was performed on the application of nanoparticles to modify orthodontic adhesives for enhancement of antibacterial or remineralization properties, but some studies also focused on the modification of orthodontic appliances with nanoparticles for surface coating or overall doping to provide antimicrobial properties. The advantage of these two approaches is that they are not dependent on patient compliance. Nanoparticle-modified fluoride varnishes and nanocarriers loaded with antimicrobial or remineralization agents may be used to promote oral health care in orthodontic patients, which have a sustained preventive effect but depend on the cooperation of the patient. It was indicated that the small size effect of nanoparticles provides better performance, but there may be certain safety issues, and there is still some influence on the physicochemical properties of the modified materials themselves. These issues must be further explored. Although there are some limitations in the current studies, nanoparticles are expected to play an important role in the prevention of enamel demineralization during orthodontics in the future.

【Key words】 nanoparticles; nano-carrier; orthodontics; enamel demineralization; white spot lesions; adhesive; appliance; oral health care; antibacterial; remineralization

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牙釉质脱矿是正畸治疗最常见的不良反应之一。正畸矫治器影响口腔清洁能力，易导致菌斑堆积及口腔菌群失调，致龋菌产酸造成牙釉质脱矿，表现为釉质表面的白垩色病损，即白垩斑(white spot lesions，WSLs)。这不仅影响美观，且可能发展为龋齿，危害口腔健康。因此，预防釉质脱矿是口腔正畸领域研究热点之一。常见预防方式有患者自我口腔保健、定期复诊进行专业清洁、使用防龋制剂，以及应用生物防龋材料改性的正畸矫治器及相关材料等。

纳米粒子(nanoparticles，NPs)通常指直径为1～100 nm的固体颗粒，具有大比表面积、高电荷密度以及强化学反应活性等特性，受到口腔医学研究人员的广泛关注[1]，为正畸釉质脱矿预防提供新策略。用于预防正畸釉质脱矿的NPs按其功能可分为抗菌、再矿化及载体型三类。抗菌类NPs可抑制或灭杀致龋菌，减少产酸，降低牙釉质脱矿发生率；再矿化类NPs提供钙磷等矿物质原料，抑制釉质脱矿并促进脱矿釉质再矿化；载体型NPs不仅能负载抗菌或再矿化功能制剂，且本身可能具备预防釉质脱矿的性能。本文总结了应用NPs对正畸粘接剂、正畸矫治器以及正畸患者口腔保健用品改性以预防正畸釉质脱矿的相关研究，以帮助读者了解相关领域的最新研究进展。

1 NPs改性正畸粘接剂

固定矫治技术在正畸治疗中应用广泛，正畸附件稳定持久的粘固是保证固定矫治顺利进行的前提。

在保证机械性能的前提下改性正畸粘接剂，赋予其抗菌或再矿化等性能，是预防牙釉质脱矿的有效手段。NPs可以用于水门汀、复合树脂、树脂-水门汀复合物三类正畸粘接剂改性[2]。

1.1 NPs改性水门汀

水门汀是指由金属盐或其氧化物作为粉剂与水或专用液剂调和后能凝固的一类材料，目前正畸治疗最常用是玻璃离子水门汀(glass ionomer cements，GIC)，具有极好的生物相容性及氟化物释放/再摄取性能，但GIC无长期防龋作用[3]。用再矿化制剂纳米羟基磷灰石(hydroxy apatite nano particles，HANPs)改性后GIC有可能显著降低正畸治疗过程中牙釉质脱矿程度[4]。

氧化锌纳米粒子(zinc oxide nanoparticles，ZnONPs)具有光催化杀菌活性，抗菌谱广、细菌耐

药性低且生物相容性好。有研究表明ZnONPs在不影响材料机械性能的同时可显著抑制致龋菌，但Garcia等[5]的研究显示，低浓度（≤ 2%wt.）的ZnONPs不能增强GIC对变形链球菌（*Streptococcus mutans*，*S.mutans*）的抗菌作用，这可能因为GIC本身有一定抗菌活性。

氧化镁纳米颗粒（magnesium oxide nanoparticles，MgONPs）能通过产生活性氧杀灭细菌，其高pH值能促进釉质再矿化，加入2.5%wt.MgONPs可提高GIC对*S.mutans*和远缘链球菌（*Streptococcus sobrinus*，*S. sobrinus*）及其生物膜的杀灭性能[3]。

1.2 NPs改性复合树脂

复合树脂由可聚合树脂单体和无机颗粒填料组成，几乎无预防牙釉质脱矿的性能[6]，应用NPs，包括金属及金属氧化物NPs、纳米天然抗菌制剂、含氟NPs、无定形磷酸钙纳米粒子（nanoparticles of amorphous calcium phosphate，NACP）等改性复合树脂粘接剂，具有一定临床价值。

1.2.1 金属及金属氧化物NPs 银纳米粒子（silver nanoparticles，AgNPs）具有低细菌耐药性和广谱、强效、持久的抗菌活性，已在口腔医学领域广泛应用。研究发现利用原位生成AgNPs技术研制的新型抗菌正畸带环粘接剂与对照组力学性能相当，能可控地持久释放Ag^+，显著抑制*S.mutans*和嗜酸乳杆菌（*Lactobacillus acidophilus*，*L.acidophilus*）[7]。加入0.33%wt.AgNPs水溶液的粘接剂能接触抑制*S.mutans*，无Ag^+释放，这使粘接剂抗菌效应更持久，该粘接剂的抗剪切粘接强度（shear bond strength，SBS）有所下降，但仍能满足临床需求[8]。混入0.3%wt.AgNPs的粘接剂具有显著非接触抗菌活性[9]。HANPs可作为载体制备AgNPs均匀分散的复合材料，在正畸粘接剂中添加5%wt.AgNPs/HANPs不影响抗剪切粘接强度且能显著抑制*S.mutans*的生长而对非致龋性血链球菌（*Streptococcus sanguis*，*S. sanguis*）的抑菌作用较弱[10]。

二氧化钛纳米粒子（dioxide titanium nanoparticles，TiO_2NPs）是一种优良的光催化抗菌剂，但所需比例较AgNPs高。在复合树脂中加入1%wt.和5%wt.的TiO_2NPs可显著抑制*S.mutans*和*S.sanguis*，但对*L.acidophilus*的生物膜无影响[11]。

1.2.2 纳米天然抗菌制剂 一些天然抗菌制剂因其优越的抗菌性能与生物相容性而逐渐被广泛应用。

从姜黄根茎中提取的姜黄素（curcumin，Cur）在光活化后可产生活性氧发挥抗菌效应。其抗菌谱广，杀菌效率高，并且是ZnONPs的优良载体。对其进行阳离子改性后得阳离子姜黄素（cationic curcumin，cCur），具有更好的抗生物膜作用，有研究发现含光活化7.5%wt.cCur/ZnONPs的粘接剂能在120 d内显著抑制多种致龋菌生物膜形成[12]。

壳聚糖是从贝类、螃蟹和虾中提取出的生物聚合物，能广谱抗菌。壳聚糖纳米粒子（chitosan nanoparticles，CSNPs）能更有效地穿透和破坏细胞膜，从而杀灭细菌。CSNPs可与其他抗菌剂协同抗菌，含10%wt.ZnONPs和CSNPs的改良粘接剂对生物膜和游离*S.mutans*、*S.sanguis*和*L.acidophilus*均有非接触抗菌效应[13]。

从蜂蜡中提取的蜂胶能够增加微生物细胞膜的通透性，抑制三磷酸腺苷（adenosine triphosphate，ATP）的产生以及降低细菌移动性[14]。含有2%wt.蜂胶NPs的粘接剂能显著抑制*S.mutans*和*S.sanguis*生物膜形成，当比例达5%wt.，对*L.acidophilus*也有显著抑制作用[15]。

1.2.3 含氟NPs 氟化物是最常用的防龋材料，既能抑制致龋菌代谢，也能抑制牙釉质脱矿、促进釉质再矿化[16]。

一种新型可充电的含氟化钙纳米粒子（nanoparticles of calcium fluoride，$nCaF_2$）的粘接剂有望实现长期高水平的F^-释放[16]。F^-本身不是高效抗菌剂，一些防龋指南建议将其与其他抗菌剂联用[17]，如有研究将具有抗菌作用的金属钇与F^-复合，混入1%wt.氟化钇NPs的树脂粘接剂表现出显著抗菌效果[18]。

1.2.4 NACP 含有NACP的树脂粘接剂钙磷离子释放率高，再矿化能力强，且能迅速中和脱矿溶液，降低牙釉质脱矿率[19]。

将40%wt.NACP混入一种新型树脂基体，可实现反复钙磷离子充电[19]。此外，NACP还可与抗菌功能制剂联合改性正畸粘接剂，能降低釉质脱矿程度，且不影响抗剪切粘接强度[20]。

1.3 NPs改性树脂-水门汀复合物

树脂-水门汀复合物主要指树脂增强玻璃离子

水门汀(resin - modified glass - ionomer cements, RMGIC),其具备释氟能力,但预防牙釉质脱矿作用有限,利用NPs改良RMGIC具有潜在的临床意义。

研究表明,添加0.1%wt.AgNPs的RMGIC同时具有接触和非接触抗菌作用[21]。在RMGIC中加入1%wt.和1.5%wt.的季铵盐聚乙烯亚胺NPs可持续抑制*S.mutans*[22]。加入20%wt.nCaF_2和3%wt.季铵盐抗菌单体甲基丙烯酸十六烷基二甲胺(dimethylaminohexadecyl methacrylate, DMAHDM)的粘接剂抗菌与再矿化性能均明显提高,且其抗剪切粘接强度和生物相容性未受影响[23]。同时添加了NACP和DMAHDM、蛋白黏附抑制剂甲基丙烯酰氧乙基磷酸胆碱的粘接剂,在体外模拟生物脱矿环境下,预防托槽周围釉质脱矿效果显著[24]。

2　NPs改性正畸矫治器

细菌在弓丝上的黏附主要取决于弓丝的表面自由能和表面粗糙度(Ra)。

在NiTi丝上制备稳定、附着力良好的ZnONPs涂层后,摩擦力降低,对*S.mutans*有显著抗菌活性[25]。

临床试验发现TiO_2NPs涂层可在初期使NiTi的Ra值降低,抑制*S.mutans*的黏附,但牙釉质脱矿预防效果不显著[26]。掺杂改性TiO_2NPs可提高其光催化性能,氮掺杂TiO_2NPs涂层托槽能在可见光下显著抑制多种口腔致病菌[27],对*S.mutans*的抑制作用至少维持90 d[28]。

涂附AgNPs的托槽[29]、正畸带环[30]以及掺杂AgNPs的弹性结扎丝[31]、活动矫治器[32]都能显著抑制致龋菌,但需进一步研究AgNPs对矫治器其他性能的影响。

3　NPs改性正畸患者的口腔保健用品

正畸矫治器的存在影响口腔卫生清洁,科学的口腔保健是维持正畸治疗期间口腔健康的有效途径。NPs可用于牙膏、漱口水、保护漆等口腔保健用品的改性,增强其预防牙釉质脱矿的作用。

3.1　氟保护漆

氟保护漆的应用是常见防龋方式,临床研究发现,固定正畸矫治患者定期用氟保护漆可一定程度预防白垩斑[33]。氟化物通过促进菌斑/牙界面再矿化及抑制链球菌产酸发挥防龋作用,但本身不是高效抗菌剂,与其他抗菌剂联用更利于防龋[17]。

与氯己定和氟化银二胺相比,一种含AgNPs、壳聚糖和氟化物的保护漆,即纳米银氟化物(nano silver fluoride, NSF),能以更低剂量抗*S.mutans*,且不影响牙齿颜色[34]。另有研究发现含CSNPs的氟保护漆对*S.mutans*的抗菌作用显著优于含5%wt. NaF的保护漆,且抗脱矿能力较强[35]。

3.2　纳米载体

聚乙二醇-聚(β-氨基酯)[Poly(ethylene)glycol-poly(β-amino esters), PEG-PAE]纳米颗粒能通过酯键与抗菌药物结合,对生物膜中的细菌具有靶向性,能直接诱导细菌裂解,同时细菌酶破坏酯键释放抗菌剂。正畸治疗患者口腔生物膜细菌的体外杀灭实验结果显示,应用PEG-PAE纳米颗粒作为抗菌剂三氯生的载体,能在较低浓度下对*S.mutans*选择性杀灭[36]。

羧甲基壳聚糖(carboxymethyl chitosan, CMC)是一种壳聚糖衍生物,能抑制生物膜形成,也是无定形磷酸钙(amorphous calcium phosphate, ACP)的载体与稳定剂。CMC/ACP纳米复合物能促进牙齿再矿化,也能抑制致龋菌粘附和生物膜形成[37]。负载ACP及抗菌剂嵌合溶菌素ClyR的CMC纳米凝胶CMC-ACP-ClyR抗生物膜效果显著,能显著降低牙釉质脱矿程度[38]。

4　结语与展望

回顾相关文献,用于预防正畸釉质脱矿的NPs按其功能可分为抗菌、再矿化及载体型三类。应用NPs改性正畸粘接剂的研究众多,包括利用纳米级别的金属及金属氧化物、天然抗菌剂、氟化物以及具备释放钙磷离子能力的再矿化制剂对正畸粘接剂进行改性,赋予其一定的预防牙釉质脱矿的性能。也有研究聚焦于利用NPs对正畸矫治器进行表面涂层或整体掺杂改性使其具备抗菌性能,该改性方式在固定和活动矫治中均能有效应用。上述两种方式的优势在于不依赖患者的依从性。此外,NPs改性的氟保护漆以及负载抗菌制剂或再矿化制剂的纳米载体可用于促进正畸患者的口腔

保健,该途径能够发挥持续的预防作用,但依赖患者的配合。

NPs的小尺寸效应,使其预防釉质脱矿的性能较常规尺寸的粒子更佳,但可能存在一定安全性问题[39],且仍对改性后材料本身理化性能有一定的影响,这些问题还需进一步探索。虽然现有文献以体外研究为主,部分研究实验周期较短,存在一定的局限性,但可以预见,未来NPs在正畸釉质脱矿的预防中有望发挥重要作用。

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