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镁涂层修饰的多孔钛合金骨科植入物研究进展

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摘　要

多孔钛合金作为一种生物惰性材料，表面缺乏有效的生物活性成分，骨整合性不足。表面改性是提升其骨整合性的有效策略。镁作为人体必需微量元素，其离子可显著促进成骨作用，但纯镁耐腐蚀性差与力学强度低，这限制了其应用。将镁以涂层形式修饰于多孔钛合金表面，可结合两者的优势，但目前尚未见相关临床应用的系统性报道。本文综述了镁涂层修饰的多孔钛合金骨科植入物研究进展，重点探讨其在骨整合促进、促血管生成及感染风险降低等方面的潜力，并分析其安全性及制备工艺，以期为临床转化提供理论支持。

关键词

镁涂层，骨整合，多孔钛合金，生物活性

Advancements in Research on Magnesium-Coated Porous Titanium Alloy Orthopedic Implants

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Abstract

Porous titanium alloys, as bioinert materials, lack effective bioactive components on their surfaces, resulting in insufficient osseointegration. Surface modification is an effective strategy to enhance their osseointegration. Magnesium, an essential trace element in the human body, can significantly promote osteogenesis through its ions. However, pure magnesium suffers from poor corrosion resistance and low mechanical strength, limiting its application. Modifying the surface of porous

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titanium alloys with magnesium in the form of a coating can combine the advantages of both materials, yet systematic reports on related clinical applications are currently lacking. This article reviews the research progress on magnesium-coated porous titanium alloy orthopedic implants, focusing on their potential to enhance osseointegration, promote angiogenesis, and reduce infection risk. It also analyzes their safety and preparation processes, aiming to provide theoretical support for clinical translation.

Keywords

Magnesium Coating, Osseointegration, Porous Titanium Alloy, Bioactivity

1. 引言

在骨科领域，四肢大段骨缺损的修复一直是临床面临的重要挑战。随着材料科学的发展及加工工艺的进步，个性化医疗器械在临床治疗中的应用日益广泛，特别是 3D 打印技术的出现为制造个性化多孔钛合金假体提供了新方法。但钛合金表面生物活性低，骨传导能力不足，孔隙深部的骨长入困难[1] [2]。为了解决这一问题，研究者开始探索各种表面改性技术，以提高钛合金的骨诱导能力。镁离子可通过调控成骨细胞分化、血管生成及免疫微环境，促进骨再生[3] [4]。然而，纯镁植入物因降解速率快、力学性能不足难以直接应用。将镁作为涂层修饰钛合金表面，既能保留钛的结构优势，又可赋予其生物活性，成为当前研究热点。本文系统分析该技术的制备方法、生物功能、安全性及临床应用挑战，旨在为未来研究提供方向。

2. 用于制备镁涂层修饰的多孔钛合金工艺

多孔钛合金表面镁涂层的制备工艺可分为三种：物理修饰、化学修饰和混合修饰。物理修饰方法主要包括：喷砂、火焰喷涂、真空等离子喷涂(Vacuum Plasma Spraying, VPS)、离子体浸没式离子注入、浸泡法等。喷砂使用氧化镁颗粒高速冲击钛表面，形成粗糙的多孔结构，能够增加表面粗糙度，但可能残留喷砂颗粒[5]。火焰喷涂将镁化合物(如 $Mg(OH)_2$ 溶液)通过火焰熔化并喷涂至钛表面，可形成较厚涂层(1~30 μm)，但结合强度较低[6]。VPS 在真空环境下，通过等离子体将镁硅酸盐(Mg_2SiO_4)粉末喷涂至钛表面，这种涂层结合强度高(41.5 MPa)，但需高温操作[7]。离子体浸没式离子注有等离子体源离子注入(Plasma Source Ion Implantation, PSII)和等离子体浸入离子注入(Plasma Immersion Ion Implantation, PIII)，通过离子束将镁等离子体注入钛表面，形成纳米级薄膜(10~60 nm)，能精确控制涂层成分，但设备成本高[8]-[10]。浸泡法将钛植入物浸泡于 $MgCl_2$ 溶液中，使镁离子沉积至表面，此方法操作简单，但需结合介孔涂层提高负载效率[9] [11]。化学修饰方法有：碱热处理、水热处理、电泳沉积、微弧氧化(Microarc Oxidation, MAO)、等离子电解氧化(Plasma Electrolytic Oxidation, PEO)。碱热处理法是用强碱溶液(如 NaOH)蚀刻钛表面，随后高温处理形成纳米结构，再浸渍镁离子，但这样可能降低假体的力学稳定性[12]。水热处理在高压反应釜中，通过水热反应生成 $Mg(OH)_2$ 纳米结构涂层，制作出来的涂层均匀且生物活性高，但操作方式比较复杂[13]-[17]。MAO 通过电化学氧化在钛表面生成含镁的多孔氧化钛层，该涂层结合强度高(30 MPa)，孔隙率可控(19%~31%) [9] [18] [19]。PEO 在含镁电解液中通过等离子放电生成 Mg-TiO_2 复合涂层，形成的多层结构(致密层 + 多孔层)，生物相容性优异[9] [20]。电泳沉积在电场作用下，将纳米羟基磷灰石(Hydroxyapatite, HA)

与镁离子共沉积至钛表面，这种方法成本低，但涂层较薄(<200 nm) [21] [22]。混合修饰有水热处理 + 离子注入、介孔涂层 + 浸泡法等。水热处理 + 离子注入先通过水热法生成纳米结构，再注入镁等离子体，这两种方式结合协同增强表面活性和力学性能[23]。介孔涂层 + 浸泡法在钛表面制备介孔 TiO_2 层，随后浸泡于 $MgCl_2$ 溶液中负载镁离子，虽能提高镁离子缓释能力，但长期稳定性需验证[24]-[26]。

3. 镁涂层修饰多孔钛合金的生物学性能

3.1. 促进骨整合

镁涂层通过镁金属降解产生的镁离子可促进血管生成、免疫调节和抗炎作用以及增强细胞迁移和粘附[27] [28]。镁离子通过整合素家族(介导细胞粘附的跨膜蛋白)和 Fak 相关信号通路之间的结合相互作用促进细胞黏附，通过激活 ERK/c-Fos、PI3K、Notch、经典 Wnt、BMP-4 相关信号通路和 TRPM7 蛋白通道诱导骨整合[9] [29]。骨髓间充质干细胞的成骨分化是镁离子调节骨再生的主要途径，可通过激活 MAPK/ERK 信号通路[30]和经典 Wnt 信号通路[29]，促进骨髓间充质干细胞成骨分化，并且具有浓度依赖性。有研究报道，10 mmol/L 镁离子通过经典 Wnt 信号通路诱导骨髓间充质干细胞成骨分化，而(2.5~5.0) × 10^{-3} mol/L 通过激活 MAPK/ERK 信号通路诱导骨髓间充质干细胞成骨分化[29] [31]。镁离子还可影响其他细胞分泌细胞因子促进间充质干细胞成骨分化。例如，对于神经细胞，促进其分泌降钙素相关肽，从而促进骨膜干细胞成骨分化增强[32]。对于成骨细胞，激活成骨细胞内 TRPM7/PI3K 信号通路，促进细胞增殖[33]。对于巨噬细胞，镁离子可以促进 M1 型巨噬细胞向 M2 型巨噬细胞转化，抑制促炎因子 TNF-α、IL-1β 及 IL-6 的分泌，促进 BMP-2 和 TGF-β 的表达，促进骨再生[34]-[36]。Yao 等人通过水热处理制备的生物活性氢氧化镁薄膜，发现其纳米结构能够释放镁离子，激活 BMP-4 相关信号通路，从而促进成骨作用[15]。综上所述，镁离子可以通过多个路径促进骨再生，不同的镁离子浓度可能激活不同的信号通路，促进间充质干细胞增殖、黏附及成骨分化。但目前最佳的浓度范围还尚不明确，高浓度还可能抑制骨再生，这些都还需进一步探索。

3.2. 促进血管生成

血管能够运输营养物质，因此血管的形成在骨生成过程中非常重要。有研究报道镁离子能够在体内共同促进血管和骨生长[37]。KUSUMBE 等人发现 H 型血管为骨骼特有的血管，骨祖细胞选择性聚集在此型血管周围[38]。Wei 等人将与镁离子螯合的聚多巴胺(PDA)涂层涂覆在 3D 打印多孔聚醚醚酮(PEEK)支架表面，研究发现该支架释放的镁离子可上调人脐静脉内皮细胞(Human Umbilical Vein Endothelial Cells, HUVECs)中 H 型血管标记物 CD31 和 EMCN 的表达，促进血管生成[39]。Gao 等人的研究发现镁涂层 Ti6Al4V 支架能促进 HUVECs 增殖、黏附、迁移，降解产生的镁离子可能通过激活低氧诱导因子-1α (Hypoxia-Inducible Factor-1α, HIF-1α)转录活性，促进血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)表达来发挥促血管生成作用[40]。这些研究充分说明，镁离子可以促进血管生成，在骨修复材料的血管化过程中意义重大，为提升骨修复效果提供了有力支持。

3.3. 减少感染风险

镁涂层还具有一定的抗菌、抗炎性能，一定程度上可以降低术后感染风险。有研究报道镁能够下调炎症相关基因 IL-1β、IL-6、TNF-α 的表达，上调抗炎基因 IL-10 等的表达[11] [14] [17] [20] [41]。此外，镁对金黄色葡萄球菌具有抗菌特性，可以阻止细菌附着和生物膜的形成[42] [43]。

4. 镁涂层修饰的多孔钛合金植入物的安全性

含镁植入物在体内降解时会产生镁离子、氢气并导致碱性环境，若降解的速率超过周围组织的代谢

能力则会导致毒副作用。人体内的多余的镁通过肾脏代谢，从尿液中排出体外。每天大约有 2400 毫克的镁被肾小球过滤，经过肾小管重吸收约 95%~99%，剩余的镁离子通过尿液排出体外[44]。镁基合金材料的细胞毒性实验，在 Wang 等[45]建议修改可生物降解镁基材料现行细胞毒性试验标准前，已有大量动物体内实验及可降解镁基植入物的临床评估表明，镁基植入物的降解产物在整个治疗期间中在体内可以耐受[46] [47]。但是，根据之前 ISO 10993 系列标准中记录的体外细胞毒性试验设计时没有考虑体内循环对降解产生的离子有清除作用，这可能导致体外和体内研究的离子浓度不一致[48]-[50]，体外研究时使用的镁离子浓度高于体内，因此使用修改后的标准，镁基合金材料的安全性更高。Zheng 等[51]将高纯镁和镁基合金植入慢性肾病模型的大鼠体内，在心脏、肝脏、脾脏、肺部或肾脏等主要器官中没有观察到镁离子浓度显著升高，在长期随访中未观察到对慢性肾病大鼠造成额外健康风险。而镁涂层修饰的 3D 打印个性化多孔钛合金四肢骨假体中镁元素的含量低于镁基合金材料中的镁元素含量，因此该涂层假体相对安全。并且 Li 等人的研究[52]发现镁涂层修饰的多孔钛合金材料在体外降解时 4 天内腐蚀速度较快，4 天后腐蚀速度较为缓慢稳定，并且初步证明了生物功能镁涂层可以促进骨整合，并且没有明显的镁腐蚀副作用。

5. 临床应用现状

目前生物功能镁涂层 3D 打印多孔钛合金支架仍处于临床前期阶段，骨科尚无有关应用于临床的报道。Li 等人[52]采用电弧离子镀的方法在 3D 打印多孔钛合金表面成功制备了具有生物活性的镁涂层，MC3T3-E1 (小鼠胚胎成骨细胞前体细胞)细胞的体外毒性和增殖研究表明，镁涂层修饰的 3D 打印多孔 Ti6Al4V 支架具有良好的降解和生物相容性。体内研究发现在植入兔股骨髁缺损 4 周和 8 周后可显著促进骨再生，具有比裸多孔钛合金更好的成骨性和骨整合性。Gao 等人[40]使用镁涂层修饰的 3D 打印多孔 Ti6Al4V 支架体进行研究表明，与裸 3D 打印多孔 Ti6Al4V 支架共培养相比，镁涂层修饰的 3D 打印多孔 Ti6Al4V 支架与 MC3T3-E1 细胞共培养可以改善细胞增殖、粘附、细胞外基质(ECM)矿化和碱性磷酸酶(ALP)活性；体内研究表明，植入后兔子的新骨再生显著增加。以上研究都表明，生物活性镁涂层修饰的 3D 打印多孔 Ti6Al4V 支架具有更好的骨整合和成骨功能，有望用于骨科应用。

6. 挑战与展望

随着 3D 打印技术和生物材料科学的不断进步，镁涂层修饰的 3D 打印个性化多孔钛合金植入物有望在临床治疗中发挥更大的作用。通过深入研究镁涂层的作用机制和优化其制备工艺，有望开发出更加安全、有效和个性化的骨修复材料，为骨缺损患者提供更好的治疗选择。尽管镁涂层修饰的 3D 打印多孔钛合金植入物在临床应用中展现出诸多优势，但仍面临一些挑战。目前关于镁涂层修饰假体的临床效果和安全性数据仍然有限，大多数研究还处于动物实验阶段，临床上骨科尚无有关临床应用数据，需要进一步的临床试验来验证其应用的可靠性。此外，镁涂层的制备工艺和质量控制也需要进一步优化，以提高涂层的均匀性和稳定性。

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