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· 综述 ·

低强度脉冲超声促进牙种植体骨结合的研究进展

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【摘要】 如何有效促进牙种植体骨结合是临床亟待解决的问题。低强度脉冲超声（low-intensity pulsed ultrasound，LIPUS）在促进骨组织在内的组织愈合中显露了优异的效果，近年来，其在促进口腔种植体骨结合方面也有较多研究。动物实验结果显示LIPUS展现出了显著的促进种植体骨结合能力。体外实验结果显示LIPUS可通过加强成骨关键因子表达、胞外基质的矿化、诱导局部神经元分泌降钙素基因相关肽（α-calcitonin gene-related peptide，αCGRP）等机制，并通过调控骨形态发生蛋白/Smad蛋白（bone morphogenetic protein/Smad，BMP/Smad）、丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）、磷脂酰肌醇3激酶/蛋白激酶B（phosphatidylinositol 3-kinase/protein kinase B，PI3k/Akt）通路等来增强骨形成细胞的增殖、迁移和成骨分化等生物学过程，从而促进种植体骨结合。同时也有临床研究显示，LIPUS治疗后种植体周围骨量均有所增加，且颊侧骨板的生长比腭侧更明显。目前尚未有研究系统性地总结LIPUS在促进种植体骨结合中的临床研究证据、体内体外研究和作用机制。因此本综述旨在讨论LIPUS对种植体骨结合的作用机制，进一步提高种植义齿修复治疗的效果。

【关键词】 低强度脉冲超声；　牙种植体；　骨结合；　骨髓间充质干细胞；　骨形成；　骨质疏松症；　降钙素基因相关肽；　丝裂原活化蛋白激酶

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Research progress on low-intensity pulsed ultrasound in promoting osseointegration of dental implants

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【Abstract】 How to effectively promote osseointegration of dental implants remains a pressing clinical challenge. Low-intensity pulsed ultrasound (LIPUS) has demonstrated remarkable efficacy in accelerating the healing of various bodily tissues, including bone tissue. In recent years, there has been extensive research on its application in promoting osseointegration in the field of dental implantology. Animal studies have shown that LIPUS exhibits significant potential in facilitating osseointegration of dental implants. *In vitro* experiments have further revealed that LIPUS can enhance the expression of key osteogenic factors, extracellular matrix mineralization, and induce local neurons to secrete αCGRP. Through the regulation of signaling pathways such as bone morphogenetic protein/Smad (Bmp/Smad), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase/protein kinase B (PI3k/Akt), LIPUS promotes the proliferation, migration, and osteogenic differentiation of osteogenic-related cells, thereby enhancing osseointegration of dental implants. Additionally, clinical studies have shown that bone mass increases around the implants after LIPUS treatment,

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with more pronounced growth observed on the buccal bone plate than on the palatal side. Furthermore, there is a lack of research that systematically summarizes the clinical evidence, in vitro and in vivo studies, and mechanisms of action regarding the role of LIPUS in promoting osseointegration of implants. Therefore, the aim of this study is to discuss the mechanisms of effect of LIPUS on osseointegration of implants, with the goal of further enhancing the outcome of implant-supported prosthodontic treatment.

【Key words】 low-intensity pulsed ultrasound (LIPUS); dental implants; osseointegration; bone marrow stromal stem cells; osteogenesis; osteoporosis; α-calcitonin gene-related peptide; mitogen-activated protein kinase

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随着口腔种植技术的发展，种植义齿成为患者首选的修复方案，其长期成功依赖于种植体良好的骨结合[1]。骨结合始于骨诱导，随后是骨生长及骨重塑，这个过程需要 3 ~ 5 个月的时间[2-3]，其效果受种植体周围骨质、骨量、种植手术方式等因素的影响[4-5]。如何进一步促进骨结合是临床上亟待解决的问题。在过去数十年里，许多研究者致力于探索促进骨结合的方法，例如种植体表面改性[6-7]，应用系统性药物[8-9]，还有各类物理刺激，如低幅度高频率振动波[10]以及低强度脉冲超声（low-intensity pulsed ultrasound，LIPUS）等。

LIPUS是一种采用低强度（一般小于100 mW/cm^2），以脉冲波方式输出的超声形式[11]，具有低免疫原性、低毒性、无创性等优点[12]。LIPUS 在促进包括骨组织在内的组织愈合中显露了优异的效果[13-14]，近年来也有学者对 LIPUS 促进牙种植体骨结合的效果和机制开展了研究。本文就 LIPUS 的生物学效应，促进组织愈合及在口腔种植体骨结合领域的研究和应用情况进行综述，为今后将其用于临床促进牙种植体骨结合提供参考。

1　LIPUS 的生物学效应

1.1　热效应

超声波传播时，介质吸收其声能并转化为热能致使温度上升[15]。在物理治疗中，超声波的热效应被广泛用于缓解疼痛、加速伤口愈合等。然而，LIPUS 由于其低强度并以脉冲形式输出，产生的热能非常有限，因此其热效应可忽略不计[16]。

1.2　非热效应

1.2.1　空化效应　空化效应是指在液体中声压使空化气泡发生膨胀和塌陷，包括稳定空化和惯性空化。稳定空化是指在较低声压下产生的空化泡，其大小在其平衡尺寸附近振荡，生成周期达数个循环。而惯性空化涉及气泡的不稳定振荡，它能够产生各种惯性力，如破碎、喷射和冲击波[17]，主要用于癌症治疗[18-19]。但在超声波治疗中，维持稳定空化效应更有效[20]。

1.2.2　机械效应　机械效应主要包括声流和传质增强。声流为超声场中能够引起局部粒子位移和流体流动的辐射力，可分为宏观流动和微观流动[21]。宏观流动是指液体中与超声波传播方向一致的流体运动。相比之下，微观流动是在振荡点附近形成小涡流，并有影响细胞膜通透性、离子扩散、细胞分泌的潜力。

传质增强是指超声波提高物质在介质中的传递效率，这一现象在接受 LIPUS 处理的细胞和组织中尤为显著。气泡振荡产生的微流引导反应物向酶活性位点或细胞移动，有助于生物活性物质释放到介质中，并产生明显的生物学效应[22]。

2　LIPUS 对组织愈合的作用

近年来，研究者们发现 LIPUS 能有效促进多种组织愈合，包括骨折、软组织再生等。最初，美国食品药品监督管理局（food and drug administration，FDA）分别于 1994 年和 2000 年批准将 LIPUS 用于治疗新鲜骨折和骨折不愈合[23]，临床数据证实 LIPUS 在加速骨折愈合中的应用是一种安全、有效的治疗方法[24]。此外，LIPUS 治疗还可促进肌腱愈合、韧带愈合和软骨修复[25]。在动物损伤跟腱模型中，LIPUS 显著增加成熟胶原纤维的数量和厚度[26]。口腔颌面部涉及软、硬两种组织成分，LIPUS 在口腔颌面部领域的应用虽然起步较晚，但已被证明同样有效。研究显示 LIPUS 能有效促进正畸牙齿移动[27-28]、牙髓再生[29]、颞下颌关节改

建[30-31]、牙周组织和口腔黏膜的修复等[11, 32-33]。

不仅如此，LIPUS还能够通过调节炎症促进组织愈合。Feltham等[34]在大鼠骨关节炎模型中发现LIPUS能减少膝关节滑膜中的白细胞浸润。da Silva等[35]在大鼠低温损伤模型中发现，LIPUS不仅可以减少M1型巨噬细胞数量减轻炎症反应，还能增加M2型巨噬细胞数量加速组织修复。以上研究结果有力地说明了LIPUS在促进组织愈合方面的显著效果。

3　LIPUS促进种植体骨结合的动物实验研究

3.1　LIPUS促进正常生理状况下种植体骨结合的动物实验研究

2008年，Ustun等[36]首次报道了LIPUS在种植领域应用的研究，其证明了频率1.5 MHz，强度30 mW/cm^{2}的LIPUS显著增加兔胫骨种植体的骨-种植体接触比（bone-to-implant contact，BIC）并提高其力学稳定性。之后，Liu等[37]使用强度40 mW/cm^{2}的LIPUS辐照兔的胫骨和股骨种植体，发现LIPUS治疗侧种植体骨结合开始较早，进展较快，种植体周围新生骨的质量和数量也优于对照侧。Ruppert等[38]发现LIPUS治疗可加速大鼠股骨种植体周围骨结合，显著增加种植体轴向载荷能力。这些体内实验结果初步证实了LIPUS对种植体骨结合的有益作用。

但是，上述动物实验主要局限于小型动物，由于其骨骼较薄，使得种植体的承载能力有限，且LIPUS能量易于传递到对照侧。因此Chauvel-Picard等[39]提出在猪模型上评估LIPUS促进种植体周围骨形成的能力，发现频率1 MHz，强度300 mW/cm^{2}的LIPUS能够促进骨重塑，加快骨-种植体界面的愈合过程。

另外，以上LIPUS促进种植体骨结合的实验结果都来自于动物的长骨模型，但长骨与颅面骨在组织起源、愈合时间及力学环境方面存在显著差异。为了更准确地模拟口腔种植体的情况，Jiang等[40]建立了小鼠口腔种植模型，证明了强度30 mW/cm^{2}的LIPUS治疗可以显著促进小鼠上颌骨种植体周围的骨形成，提高BIC值。EI Sharkawy等[41]证明频率3 MHz，强度40 mW/cm^{2}的LIPUS促进了犬下颌骨种植体周的骨形成并加速了骨-种植体界面的愈合过程。与长骨种植相比，上述口腔内种植的研究结果更具有临床参考价值。

以上结果显示，在不同动物模型和不同的种植位点LIPUS均展现出显著的促进种植体骨结合能力，这为LIPUS在口腔种植的临床应用奠定了基础。且Liu[37]、Ruppert[38]以及EI Sharkawy等[41]在研究中均发现，LIPUS对种植体骨结合的促进作用主要发生于种植治疗早期，表现为LIPUS治疗侧种植体周围骨增量的变化在早期较对照侧明显，以及在力学上更早达到种植体稳定性的上限。因此建议在种植体植入后早期应用LIPUS治疗，以缩短种植修复治疗周期。

上述研究采用的参数集中在频率1 ~ 3 MHz，强度30 ~ 300 mW/cm^2，结果均证明了LIPUS对种植体骨结合的促进作用，这提示LIPUS的治疗效果在动物模型身上具有较广泛的参数适用性，未来需要针对不同条件选择更精确的LIPUS参数以实现疗效最大化。

3.2　LIPUS促进病理状况下种植体骨结合的动物实验研究

全身因素如糖尿病和骨质疏松症影响种植体骨结合。正常人群的种植失败率为1% ~ 3%，而糖尿病患者种植失败率为10% ~ 20%[42]，且伴有种植体骨结合延迟以及边缘骨质流失增加[43]。骨质疏松症降低骨密度和骨矿物质含量，阻碍骨再生和骨重塑过程，从而导致种植体骨结合不良[44]。

一项最新研究显示[45]，频率1.5 MHz，强度60 mW/cm^{2}的LIPUS作用后的2型糖尿病（type 2 diabetes mellitus，T2DM）大鼠种植体周骨高度与非T2DM大鼠相似，骨形成参数均明显改善，移除扭矩测试（removal torque test，RTV）数值明显提高。Zhou等[46]建立骨质疏松症大鼠种植模型，采用频率1.5 MHz，强度40 mW/cm^{2}的LIPUS治疗，结果显示LIPUS在整个愈合周期内增加了骨再生量，且在前两周效果最明显。证实了LIPUS能够促进糖尿病和骨质疏松症状态下的种植体骨结合并增强其稳定性。

目前，关于LIPUS在病理状态下促进种植体骨结合的研究较少，因此未来需建立更多涵盖多种病理状态的动物模型，以深入探究LIPUS的影响。

4　LIPUS促进种植体骨结合的临床研究

Abdulhameed等[47]临床研究结果显示在种植体植入6个月后，LIPUS治疗组种植体周围骨量均有所增加，且颊侧骨板的生长比腭侧更明显，而对照组出现骨高度和骨宽度的减少，且LIPUS治疗组RTV和共振频率分析数值在术后6个月时均较对

照组显著增加。这一研究结果证实了LIPUS促进种植体骨结合的临床效果，并提示其可用于提高初期稳定性不佳的种植体成功率。

目前LIPUS促进种植体骨结合的临床研究匮乏，但正畸牙齿移动与种植体周围骨重塑存在诸多相似之处，包括各类细胞之间的相互作用以及骨吸收和骨生成之间的平衡[48]。正畸领域的临床研究已证实LIPUS能够加速牙齿移动，缩短治疗周期[49-50]。基于此，推测LIPUS在口腔种植领域促进种植体骨结合也能取得佳效，需进行更多大样本、多中心临床研究来验证其疗效。

5 LIPUS促进种植体骨结合的机制研究

LIPUS促进骨愈合的细胞与分子机制尚不完全清楚。骨形成细胞是成骨的主要参与者。目前的研究显示，LIPUS对骨形成细胞的增殖、迁移和成骨分化都有促进作用。An等[51]研究表明，LIPUS能够显著增强大鼠骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMSCs）在钛种植体表面的黏附与增殖能力。Hsu等[52]研究则表明LIPUS能够促进成骨细胞增殖及迁移从而促进骨结合。还有研究发现，LIPUS处理能促进BMSCs在钛酸钡涂层钛支架表面的黏附和增殖，增强了成骨分化标志基因的表达[53-54]。在细胞迁移方面，Xiao等[55]发现LIPUS上调大鼠BMSCs中基质细胞衍生因子-1α（stromal cell-derived factor-1α，SDF-1α）和趋化因子受体4（chemokine receptor 4，CXCR4）的基因表达，显著提高BMSCs的迁移和趋化性。在细胞分化方面，Kaur等[56]证明LIPUS通过产生活性氧调节MC3T3-E1细胞中成骨基因的表达以及ERK1/2信号通路的激活。此外，Maung等[57]证明LIPUS使骨膜源性细胞中的BMP-2和磷酸化Smad 1/5/9的表达明显升高，通过激活BMP-Smad经典通路促进其成骨分化。

LIPUS调节骨形成细胞的机制与多个下游通路有关。在细胞增殖方面，Gao等[58]研究发现BMSCs中的c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）信号通路被LIPUS激活。Xie等[59]研究发现LIPUS能通过激活PI3K/AKt信号通路提高人BMSCs的增殖能力。此外，Jiang等[40]发现LIPUS作用下，在含有αCGRP条件培养基中的成骨细胞的成骨关键分子显著增加，这提示诱导局部神经元生成αCGRP可能是LIPUS促进种植体骨结合的机制之一。Chen等[60]证明LIPUS上调了整联蛋白α8（integrin subunit alpha 8，ITGA8）的基因表达，并通过激活粘着斑激酶-细胞外调节蛋白激酶1/2（focal adhesion kinase-extracellular regulated protein kinases 1/2，FAK-ERK1/2）信号通路在体内、体外促进BMSCs的迁移。Matsumoto等[61]证明LIPUS通过激活初级纤毛介导的音猬因子（sonic hedgehog，SHH）信号通路刺激MC3T3-E1细胞成骨分化。

同时，血管生成在骨形成初期的血管化过程中至关重要。Kang等[62]研究发现LIPUS能够显著提高人脂肪源性干细胞与人脐静脉内皮细胞共培养系统中血管内皮钙粘蛋白mRNA的表达水平，并且有效促进体内外的血管生成。此外，Liu等[63]研究也进一步证实了LIPUS能够有效促进与成骨细胞外泌体共培养的内皮细胞增殖以及血管生成。这些研究成果都提示LIPUS可促进血管化。

此外，巨噬细胞等免疫细胞也深度参与了骨代谢。巨噬细胞与成骨细胞毗邻并支持骨形成，并在骨微环境中转换极化状态参与炎症和骨组织修复过程[64]。LIPUS调节巨噬细胞参与骨代谢的作用主要在抑炎和促进巨噬细胞极化两方面。有研究显示LIPUS通过上调巨噬细胞的自噬水平抑制白细胞介素-1β（interleukin-1β，IL-1β）的产生而改善骨关节炎[65]。

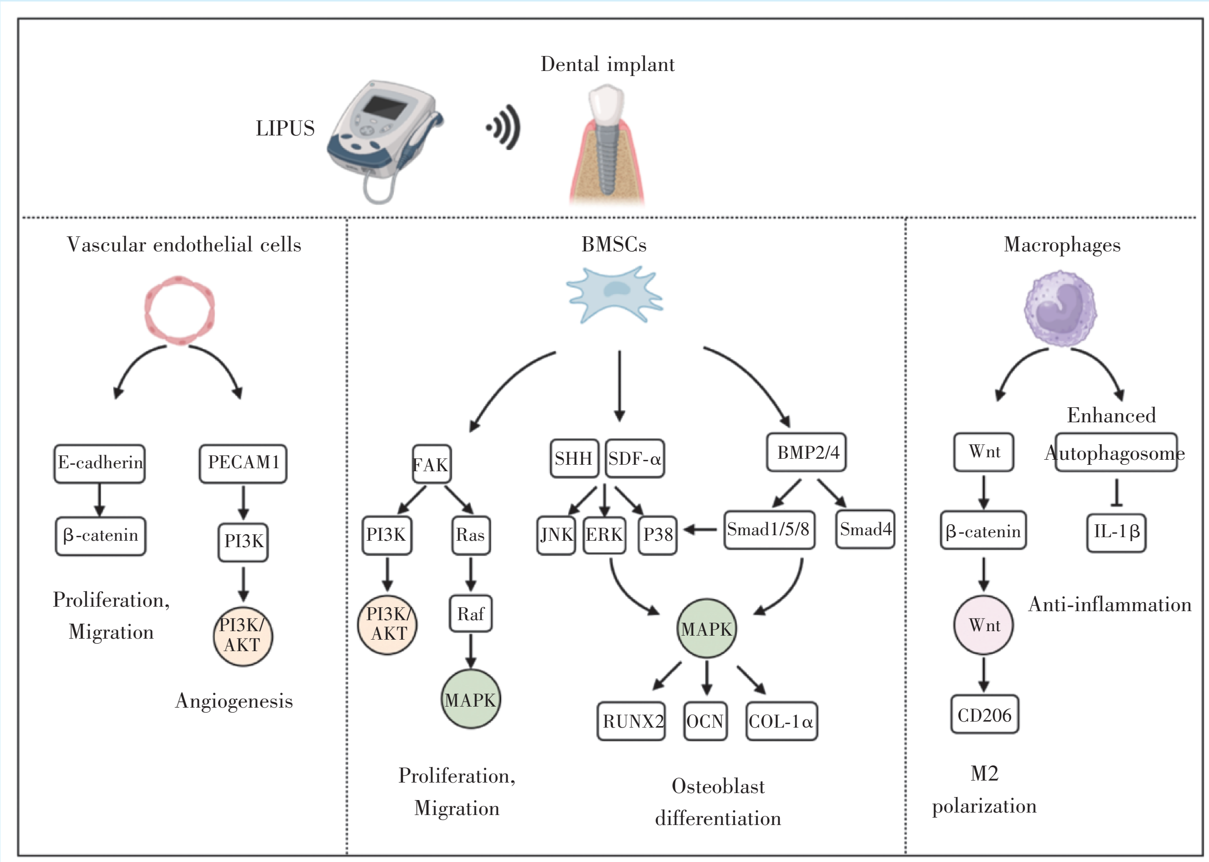
另一方面，有研究显示在LIPUS刺激下，植入小鼠皮下的支架材料周围观察到更高比例的CD206+的M2型巨噬细胞，伴随骨形成的增加[66]。同时还有研究显示，LIPUS处理组骨骼肌挫伤小鼠显示出M1巨噬细胞的清除和M2型的增加，其机制与Wnt通路有关[67]。上述研究都证明，LIPUS调节巨噬细胞的能力在骨再生以及促进种植体骨结合领域有广阔的应用前景。

本文总结了LIPUS调节主要骨生成相关细胞的可能作用机制（图1），未来需进一步深入探究其具体的信号转导机制。

6 总结与展望

LIPUS相比其他物理方法具有独特优势。其超声波能精确穿透软组织，直接作用于骨骼深层，效果优于振动波治疗。与电磁场疗法相比，LIPUS治疗温和，副作用少，适合长期重复治疗。因此，LIPUS有望成为促进牙种植体骨结合的优选治疗方法。

LIPUS可通过增强细胞增殖、迁移及成骨分化等生物学过程促进种植体骨结合，从而提高牙种



LIPUS regulates vascular endothelial cells, BMSCs, and macrophages to participate in bone formation. LIPUS: low-intensity pulsed ultrasound; PECAM1: platelet endothelial cell adhesion molecule 1; BMSCs: bone marrow mesenchymal stem cells; RUNX2: runt-related transcription factor 2; OCN: osteocalcin; COL-1α: collagen-1α; Wnt: wingless/integrated; CD206: cluster of differentiation 206; FAK: focal adhesion kinase; ERK: extracellular regulated protein kinases 1/2; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; BMP: bone morphogenetic protein; MAPK: mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; IL-1β: interleukin-1β; SHH: sonic hedgehog; SDF-1α: stromal cell-derived factor-1α

Figure 1　Molecular mechanisms by which LIPUS regulates the osteogenic microenvironment to promote bone regeneration

图1　LIPUS调节成骨微环境促进骨再生的分子机制

植体植入后的稳定性，缩短愈合周期，这对于需尽快恢复口腔功能的患者尤为有利。同时，LIPUS还能降低初期稳定性不佳导致的种植治疗失败风险，提升种植疗效和患者满意度。

尽管LIPUS在促进种植体骨结合方面效果显著，但具体机制尚未完全明确，这限制了其在临床应用的精确性。LIPUS的治疗效果受频率、强度等参数影响，因此建议开展更多临床和基础研究，探索最佳治疗参数。同时，未来需要更多研究验证其在不同人群中的效果，以实现个性化治疗。此外，LIPUS与其他方法（如种植体涂层、振动波等）结合使用时可能产生更积极的影响，因此，探索不同方法联合使用也成为了极具价值的研究方向。相信在进一步明确LIPUS的作用机制并优化治疗参数后，其有望成为口腔种植领域促进种植体骨结合的一种有效、安全、舒适的物理治疗方法，进一步提高种植义齿修复治疗的效果。

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