低强度脉冲超声治疗骨质疏松的可行性分析

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摘要 骨质疏松症是一种全身性骨骼系统疾病, 以骨量减少、骨微结构退化为主要特征, 常伴有骨痛、驼背、骨折等症状, 严重影响患者生活质量. 目前骨质疏松治疗以药物治疗为主, 但副作用较大. 物理疗法低强度脉冲超声(LIPUS)则可以避免药物不良反应, 且具有无创伤、无电离辐射等优点. 研究表明, LIPUS刺激在骨折愈合中具有积极作用, 而骨折和骨质疏松治疗时某些生物机制相似, 因此LIPUS可能是治疗骨质疏松的重要潜在手段. 本文通过查阅以“LIPUS”、“骨折”、“骨质疏松”为主题的大量相关资料并进行归纳总结, 从骨组织结构与功能、LIPUS治疗骨病的生物学机制以及LIPUS治疗骨质疏松的实验研究入手, 分析论证LIPUS治疗骨质疏松的有效依据, 对LIPUS治疗骨质疏松研究现状进行综述, 以为治疗骨质疏松提供新的思路和理论依据.

关键词 骨质疏松, 低强度脉冲超声, 骨折, 生物学机制

骨质疏松症是现代社会影响人类健康的重大问题. 它是以骨矿成分减少、骨微结构退化为特征的, 导致脆性增加、骨折风险提高的一种全身性骨骼系统疾病, 多见于中老年人群. 随着人口老龄化加剧, 骨质疏松发病率正逐年提高, 目前全世界骨质疏松症患者大约有2亿人^[1,2]. 一方面, 骨质疏松症引起的腰背疼痛和身体机能下降严重影响患者生活质量, 骨质疏松性骨折也给家庭和社会造成很大的医疗负担. 另一方面, 在失重环境下, 骨骼脱负引起的骨质疏松已成为妨碍航天员健康和太空探索能力的重要难题之一^[2]. 因此, 它的早期诊断和及时治疗具有重要意义.

超声方法具有费用低、无电离辐射、简便、速度快和可携带等优点, 在超声诊断方面受到国内外学术界和医学界的高度重视^[3~6]. 目前, 临床诊断骨质时常采用超声透射法, 但这种方法不能全面反映松质

骨质量及骨微结构信息^[3~6]; 而近几年的研究结果表明^[6~11], 超声背散射信号能有效地反映松质骨的微结构信息. 因此, 超声背散射信号评价松质骨及诊断骨质疏松症已成为近年来的一个研究热点, 并已在成人^[6,9]和新生儿^[10,11]骨质临床评价中都取得了显著的进展.

目前骨质疏松的治疗方法以药物治疗为主, 常用的药物有双膦酸盐、钙剂、维生素D、降钙素、雌激素等^[12~14], 但是药物治疗通常具有全身性作用, 副作用较大^[13,14]. 物理法则可以避免药物治疗的不良反应, 常用的物理疗法主要有超声波、磁疗、热疗等. 低强度脉冲超声(low-intensity pulsed ultrasound, LIPUS)作为对骨组织有效的力学信号, 具有无创伤、无电离辐射、价格低廉等优点. 有学者在一些骨病治疗尤其以骨折的治疗中使用LIPUS刺激, 发

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现LIPUS可以加速成骨过程^[15~21],减少骨量丢失^[22~24],这些研究成果表明,LIPUS可能是治疗骨质疏松症的重要潜在手段^[25~32].

本文从LIPUS治疗骨病的生物学机制和LIPUS治疗骨质疏松的实验研究入手,旨在分析LIPUS治疗骨质疏松的可行性,以期治疗骨质疏松提供新的理论依据和方案.

1 LIPUS治疗骨病的生物学机制

1.1 骨的结构与功能

骨组织是一种由多种细胞成分及大量钙化的细胞间质组成的结构坚实的结缔组织.骨的钙化细胞间质称为骨基质,骨基质成熟后以骨板形式存在.为适应不同力学特性,骨板排列形式有很大不同,空间结构各异,通常分为皮质骨和松质骨两大类(图1),外侧皮质骨呈管状,结构致密;内层松质骨呈蜂窝状^[33].松质骨内部布满了相互交织的立体孔状结构,称为骨小梁.骨小梁伸展方向与骨所承受的压力和张力的方向一致,众多骨小梁支撑起了多孔松质骨.皮质骨占到人体骨总量的85%,密度较大^[33,34].皮质骨微观结构使得骨骼在承重方向具有很好的强度与韧性.骨质疏松对骨几何结构的影响主要表现为:松质骨中骨小梁变细缺失,孔隙增大,皮质骨骨基质减少,髓腔体变大^[33].

人体骨骼具有生命活动,能够进行新陈代谢,其结构和形态一直处在不断变化的动态平衡中.骨的形态基本由先天基因决定,但其结构主要受后天环

图1 股骨上端冠状切面

Figure 1 The coronary section of upper femoral

境中力学因素的影响和调控,使其本身在质量、数量、分布和微结构完整性等各方面都以最优状态来适应不断变化的力学环境.骨组织这种特性被称为骨的功能适应性,自适应调整的过程被称为骨重建.

1.2 LIPUS对骨组织细胞的影响

成骨细胞和破骨细胞是骨组织的重要细胞成分.成骨细胞是骨形成的主要功能细胞,负责骨基质的合成、分泌和矿化,骨不断进行着重建;破骨细胞具有特殊的吸收功能,吸收骨基质的有机物和矿质,使其降解,释放钙离子等.破骨与成骨过程的平衡左右着骨的新陈代谢,是维持正常骨量的关键^[35,36].骨内稳态失衡导致的骨过度吸收是骨质疏松的主要病理特征.研究发现,小鼠(*Mus musculus*)骨髓基质干细胞(bone marrow stromal cells, BMSC)在一定条件LIPUS辐照下不仅可以提高早期反应基因瞬时表达,同时能够加速骨分化标记基因——骨黏连蛋白和骨桥蛋白表达.这些早期反应基因以及细胞外基质的基因跟细胞分化和增殖密切相关,提示LIPUS对成骨细胞谱系的影响^[37,38].一定强度LIPUS对大鼠(*Rattus norvegicus*)骨髓间充质干细胞(rat bone marrow stromal cells, rBMSC)成骨分化成熟有明显促进作用^[15].LIPUS作用于大鼠成骨肉瘤细胞(rat osteosarcoma, ROS17/2.8)以及动物实验研究结果显示^[17],LIPUS刺激促进成骨细胞骨生成的某些特殊活动,提高矿化沉积率^[39],导致矿化结节形成.Yang等人^[40]发现,超声刺激作用于小鼠成骨细胞株系MC3T3-E1时,在促进成骨细胞分化成熟的同时抑制了BMSC向破骨细胞分化,双向调节骨生成过程.Sun等人^[41]也发现,超声具有促进成骨细胞生成抑制破骨细胞的作用.另有研究指出^[42],破骨细胞对超声的反应跟所用剂量密切相关:低剂量的超声(重复频率为1 Hz,作用时间小于15 min)作用于FLG29.1人类细胞系时,破骨细胞增殖作用有所增强;而使用较高剂量超声(重复频率100 Hz, 1 kHz,作用时间30 min, 60 min)后则明显抑制破骨细胞生成.实验结果提示,适当剂量的超声可以抑制破骨细胞增殖从而减少骨吸收作用,达到减少骨量流失的目的.

1.3 LIPUS对细胞信号转导的影响

细胞信号转导是指细胞通过膜受体或核受体感受细胞外因子的刺激,引发细胞内一系列生物化学

反应以及蛋白间相互作用,直至细胞生理反应所需基因表达、各种生物学效应形成,从而影响细胞生物学功能的过程。众多研究显示,LIPUS对骨组织的作用很多是通过作用于细胞间信号的转导实现的^[43,44]。目前的研究普遍认为^[45,46],作为电位机械敏感信号通路的细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)在成骨分化成熟过程中起到了较大作用,p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK)确实参与成骨细胞分化过程。而在另一组LIPUS对细胞通讯影响的实验中研究人员发现^[47],施加了LIPUS刺激(20 min)的BMSC组发生明显变化,其细胞间染料扩散率大大高于空白对照组,抗磷酸化细胞外信号调节激酶1/2(anti-phosphorylated extracellular signal-regulated kinase1/2, pERK1/2)和p38磷酸化作用显著提高,碱性磷酸酶(alkaline phosphatase, ALP)活性明显增加。这些实验现象表明,LIPUS刺激通过影响pERK1/2和p38等作用于细胞间的缝隙连接通讯。细胞内离子浓度变化引起细胞膜内外电位变化也是细胞内信号传导的重要途径。Alvarenga等人^[48]所做的一组对比实验中,正常组和对照组均施加LIPUS刺激,对照组加入钙离子螯合剂及选择性P2Y受体拮抗剂,结果表明,正常组LIPUS可活化P2Y受体,细胞内嘌呤释放量增加,而使细胞内钙离子浓度增加;对照组LIPUS作用明显受到抑制。结果提示,LIPUS通过影响细胞内钙离子浓度变化诱导成骨增殖分化。Ikeda等人^[46]在探索LIPUS加速骨修复可能的内在生物学机制时发现,LIPUS刺激显著影响了Runt相关转录因子2(Runt-related transcription factor 2, Runx2)和Sox9(SRY(sex determining region Y)-box 9)等相关转录因子mRNA表达(Runx2与成骨细胞密切分化相关,Sox9与软骨细胞分化相关);同时使与肌细胞、脂肪细胞分化相关的基因mRNA表达明显下降,ERK1/2和p38MAPK活性增强。Ikeda等人据此推测,LIPUS刺激有效提高了ERK1/2和p38MAPK活性,进而把多功能间充质干细胞(C2C12细胞)的分化途径转变成了成骨细胞和(或)软骨细胞系的分化过程,这也许是LIPUS促进成骨分化的信号转导通路之一。

1.4 LIPUS对骨相关因子的影响

骨发生相关因子是骨代谢过程中的重要细胞因子,分布广泛,以自分泌和旁分泌方式在骨形成和重

塑过程中调节多种细胞分裂增殖和细胞基质合成,既有促合成代谢作用,又有促进生长作用,被认为是骨形成、骨重塑和骨修复过程中最关键的调节因子^[34,49]。因此,LIPUS治疗过程中各种骨相关因子的变化也被发现并关注。骨形态发生蛋白(bone morphogenetic protein, BMP)作为一种重要的具有很强诱导活性的骨生长因子,能够有效刺激间充质细胞诱导分化成软骨细胞、骨细胞,进而形成软骨及骨组织。实验发现,超声促进成骨细胞中BMP-2的表达,从而加速骨折愈合^[50]。Angle等人^[51]在临界性骨缺损模型实验中研究LIPUS和重组人类骨形成蛋白-2(recombinant human bone morphogenetic protein-2, rhBMP-2)在骨修复过程的作用,结果显示,和仅LIPUS照射组相比,LIPUS照射和rhBMP-2联合使用明显促进早期骨形成进程,促进愈伤组织成熟,治疗效果大大提高。这些实验表明,LIPUS和BMP在成骨过程中具有一定协同作用。转化生长因子-P(transforming growth factor, TGF-P)可以促进成纤维细胞、成骨细胞生长,抑制破骨细胞形成,是重要的骨生长刺激因子^[34,44]。有学者^[52]以LIPUS照射软骨细胞系后,发现实验组的II型胶原和蛋白多糖mRNA表达增加,2~12 h后TGF- β mRNA表达显著提高。Lai等人^[53]在细胞实验中也观察到LIPUS照射组TGF- β 的增加,提示LIPUS影响TGF-P表达及含量变化,促进成骨细胞和软骨细胞增生,诱导膜内成骨和软骨内成骨过程。碱性成纤维生长因子(basic fibroblast growth factor, bFGF)具有促进成骨细胞增殖分化和分泌胞外基质作用,主要在骨生长早期合成,是一类活跃的形态发生因子,对维持细胞表型和促进细胞增殖具有重要意义。梁伟等人^[54]在探索LIPUS在兔(*Leporidae*)桡骨骨折愈合过程中bFGF的表达及分布的实验中发现,LIPUS明显促进骨折部位bFGF表达,说明LIPUS刺激影响了bFGF形成、活化和分泌过程,进而产生了促进骨基质分泌及软骨基质钙化作用。血管内皮生长因子(vascular endothelial growth factor, VEGF)被认为是最有效的促进血管生长的因子,通过结合受体促进血管和淋巴管生长^[55]。Lu等人^[56]向髌骨切除兔子模型施加LIPUS照射,实验结果发现,LIPUS刺激能够调控成骨细胞和成软骨细胞的VEGF表达。

1.5 LIPUS对骨组织生物力学的影响

骨骼是人体的支撑系统,主要功用是运动、造

血、支持保护身体以及储藏矿物质,有着复杂的内在和外在结构.除了研究骨修复的生理学特性之外,对骨修复过程生物力学研究也不可或缺.多项实验研究均表明,LIPUS刺激能够显著改善骨密度、骨钙含量以及骨组织结构力学和材料力学等多种生物力学性能.吕红斌等人^[57]探讨LIPUS对兔四肢骨延长模型中新生骨成熟过程的影响,X线片结果显示,LIPUS治疗组新生骨的相对灰度值明显大于对照组,骨密度测量结果为8周和12周LIPUS治疗组相对骨矿密度(bone mineral density, BMD)明显高于对照组,生物力学测试结果显示,LIPUS治疗可以提高极限扭转强度、最大扭矩和破裂能,与对照组比较差异有统计学意义.各项测试结果均说明,超声治疗能显著促进新生骨成骨,提升成骨的力学性能.另有研究人员^[58]通过兔双侧桡骨分离骨折模型探究LIPUS对骨折愈合的生物力学的影响,结果显示,LIPUS治疗组可以提高骨折愈合过程中骨组织的抗弯、抗扭强刚度,并且发现在一定范围内超声治疗时间与骨折愈合的质量正相关,骨的成熟度得到改善.Uddin和Qin^[22]最新研究成果表明,LIPUS可以提高废用性骨质疏松骨组织结构的完整性,有效改善力学性能.Wu等人^[23]所做的实验结果显示,LIPUS刺激的卵巢切除(ovariectomized, OVX)组小鼠股骨湿重增加,形态学图像显示松质骨小梁数增加.推测LIPUS可以加速骨形成,防止骨质流失,可能是治疗骨质疏松的潜在手段.

2 LIPUS促进骨折愈合

自从1952年意大利学者corradic发现LIPUS刺激可以促进兔双侧桡骨骨折愈合以来,至今对LIPUS治疗骨折的研究已有60多年,学者们相继报道了众多的深入研究成果.1983年Duarte^[59]使用LIPUS来刺激骨生成,组织学分析显示,LIPUS可以加速骨痂生成,促进骨折愈合过程.Cheung等人^[60]探究LIPUS对骨质疏松性骨折的作用效果,发现LIPUS刺激可以加速愈伤组织和血管生成,促进愈伤组织重构,从而加快骨质疏松性骨折愈合过程.美国食品与药品监督委员会(Food and Drug Administration, FDA)分别于1994和2000年批准了LIPUS用于新鲜骨折和骨不连的临床治疗.美国Smith&Nephew公司已经开发出可用于骨折及骨不连治疗的低强度脉冲超声治疗仪Sonic Accelerated Fracture-Healing System, Exogen™. LIPUS

刺激作用于骨折修复的各个阶段(炎症期、软骨痂形成期、骨形成期、骨重塑期),加速骨折愈合,但是其具体作用机制尚不明确,最佳治疗参数仍待进一步探索^[61-65].Angle等人^[15]实验证实,一定参数条件下的LIPUS不仅能够积极促进rBMSC分化,还发现低于临床使用的LIPUS强度依然有效,且在效果上看,2 mW/cm²的强度较其他组(包括临床使用的30 mW/cm²)具有最佳效果.Fung等人^[66]使用临床批准的1.5 MHz, 30 mW/cm²的LIPUS刺激治疗骨折,但使用3组不同轴向距离(距离声场远近)调查其对骨折愈合过程是否会产生不一致的生物效应.结果显示,130 mm组BMD值最高,而60 mm组合0 mm组编织骨形成有所增强,结果暗示LIPUS声场的轴向距离对骨折治疗效果有一定影响.文献[25]最新研究表明,聚焦LIPUS能够提高颅骨缺损模型中的细胞增殖进而促进再骨化作用.文献[67]报告显示,在不影响ALP活性情况下,LIPUS刺激通过作用P2X7受体诱导细胞外ATP的释放,促进成骨细胞增殖和骨生成,为LIPUS治疗的具体生物作用机制进行了有益探索.

LIPUS治疗骨折及骨不连的研究表明,LIPUS刺激在骨折愈合过程中具有积极作用.而骨质疏松是以骨量流失为主要特征的骨骼疾病,和骨折治疗有相似的生物学机制.LIPUS刺激促进细胞增殖分化、加速骨钙矿化,调节相关细胞基因表达和生长因子释放,可能是治疗骨质疏松的重要潜在手段.

3 LIPUS治疗骨质疏松的实验研究

目前,LIPUS治疗骨质疏松的实验研究主要从细胞实验、动物实验和临床试验3个层面展开.3个层面相辅相成,又各有侧重,从不同角度研究LIPUS治疗骨质疏松的有效证据.

3.1 细胞实验

目前,LIPUS治疗骨质疏松的研究在细胞层面上更多的是对成骨细胞增殖分化及成骨作用的探讨.Takayama等人^[17]首次使用LIPUS治疗牙周病导致的骨质流失,其中图2表示培养基矿化结节钙含量测定结果.实验中使用1.5 MHz, 30 mW/cm²的LIPUS刺激作用于ROS17/2.8细胞,结果显示,LIPUS刺激7 d之后,ALP活性增强;PCR分析显示,Runx2, Osterix等骨相关转录因子mRNA表达显著增加;有矿化结节形成且在LIPUS刺激14 d之后矿化结节钙含量大幅增

图2 (网络版彩色)培养基矿化结节钙含量测定结果^[17]。(a) ROS细胞相衬显微照片;(b) 培养基钙含量测量。所示数据使用均值标准差表示, *: $P < 0.05$

Figure 2 (Color online) Measurement results of LIPUS treated conditioned medium on calcium content of mineralized nodules^[17]. (a) Phase-contrast micrograph of ROS cells; (b) calcium content measurement in medium. The data shown are the mean $\pm$ SD. *: $P < 0.05$

加。结果提示, LIPUS刺激促进成骨细胞骨生成的某些特殊活动, 加速骨细胞钙化过程。于海生等人^[68]利用0.6 MHz固定频率的LIPUS作用于BMSCs, 研究BMSCs增殖的可能性, 筛选实验最佳参数, 并得出结论, LIPUS辐射一定时间后能够促进BMSCs增殖, 不同辐射强度和辐照时间促进其增殖的效应不一, 其中强度为0.2 W/cm², 辐照10 min剂量促进增殖效果最佳。

LIPUS最佳治疗参数在LIPUS研究中至关重要, 但是其受到诸多因素影响。例如, 换能器的几何形状可以影响传播、反射、声压的时空比以及体施加到细胞上的超声强度; LIPUS的物理性质如频率、强度、占空比以及声波持续时间也对刺激结果有一定影响。由于不知道哪些参数是给定生物效应的主导因素,

因此细胞实验探索LIPUS最佳治疗参数的方案设计应该精确给出换能器相关参数(几何形状、中心频率、强度、占空比、峰值压强、脉冲持续时间等), 标准化LIPUS剂量。

3.2 动物实验

在动物实验方面, LIPUS用于骨质疏松治疗还处在初级探索阶段。Wu等人^[23]假设LIPUS技术可以防止骨质流失, 以卵巢切除术(OVX)制作大鼠腿骨骨质疏松模型, 分组对照实验结果显示, OVX组接受LIPUS治疗的右侧股骨湿重和骨小梁数量有增加, 一定程度上说明LIPUS可加速成骨作用, 防止骨质疏松模型中的骨量丢失。Poliachik等人^[28]采用麻醉诱发的骨质缺损小鼠模型进行实验, 使用聚焦型超声换能器施加LIPUS刺激, 结果表明, 聚焦型LIPUS能够缓和麻醉造成的骨质流失。Uddin和Qin^[22]的实验小组认为, 废用性骨质疏松是由缺乏机械刺激引起的局部病理现象, 而LIPUS则提供了一种非侵入式、靶向性的机械刺激来保持骨的形态和机械完整性, 进而对抗因废用导致的骨质流失。该实验小组通过尾吊方式制作废用性骨质疏松小鼠动物模型, 并把小鼠分为(i)年龄相匹配的正常对照组(age-matched, AM); (ii)非尾吊-假性超声治疗组(non-suspended sham, NS); (iii)非尾吊-LIPUS治疗组(non-suspended-LIPUS, NU); (iv)尾吊-假性超声治疗组(suspended sham, SS); (v)尾吊-LIPUS治疗组(suspended-LIPUS, SU)。图3表示小鼠胫骨骨小梁超声治疗效果的 μ CT评价, 图4表示小鼠注射荧光标记追踪骨微结构变化, 胫骨干骺端切片分析结果, 其中LIPUS刺激参数为脉冲重复频率1 kHz, 占空比20%, 强度30 mW/cm², 治疗时间每天20 min, 每周5 d, 共进行4周。

结果显示, 与仅尾吊的假性超声治疗组(SS)相比, LIPUS治疗组的组织矿物质密度(tissue mineral density, TMD)和骨小梁厚度(trabecular thickness, Tb.Th)显著增加, 而骨表面积体积比(bone surface/bone volume, BS/BV)下降; 骨结构完整性、骨内膜处骨形成率以及骨小梁表面积均增加; 四点弯曲力学测试显示, 与SS组相比, LIPUS刺激减轻了废用对骨的弹性模量、屈服强度和极限强度造成的不利影响。说明接受LIPUS治疗的小鼠能够保持骨微结构完整性, 提高骨形成率, 改善股骨力学性能。

在临床试验方面, 由于目前LIPUS治疗骨质疏松

图3 小鼠胫骨骨小梁超声治疗效果的μCT评价. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ ^[22]

Figure 3 Mouse tibial trabecular bone μCT evaluation of the LI-PUS treatment effect. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ ^[22]

图4 (网络版彩色)小鼠注射荧光标记追踪骨微结构变化, 胫骨干骺端切片分析结果^[22]. AM组单一标记连续, 表明其骨微结构完整, SS组几乎没有标记, 表明其骨微结构破碎, SU组股内膜和骨小梁表面两种标记明显增强, 表明其骨微结构增强

Figure 4 (Color online) Mice were injected with a fluorescent marker to track changes in bone microstructure, analyses were performed on proximal tibia metaphyseal sections^[22]. AM mice showed intact microstructure along with seamless single labeling, SS mice showed broken down microstructure with little or no labeling, and SU mice showed improved microstructure and with enhanced double labeling along endosteal and trabecular surfaces

的研究有待深入, 因此尚未见比较可靠的临床治疗方案和相关统计数据. 但是LIPUS用于加速骨折愈合

的临床案例比较常见, 也可间接说明LIPUS能够促进骨生长, 是治疗骨质疏松的潜在有效手段.

4 结论和展望

骨质疏松症是一种骨量下降, 骨微结构退化, 骨力学特性衰退的全身性骨质疾病。骨质疏松是逐渐变化的过程, 极易被患者忽视, 但若不及时治疗, 将会导致骨骼变脆, 骨折风险大大增加。实验证实, LIPUS对骨细胞增殖分化和成熟以及骨质矿化具有显著效应, 对细胞信号转导和骨代谢过程中的重要细胞分子具有促进作用, 并且能够显著改善骨密度、骨钙含量以及骨组织结构力学和材料力学等多种生物力学性能。但总体来说, 这方面的研究仍存在许多问题有待解决。

(1) LIPUS治疗骨质疏松的研究目前处于初步阶段, 研究层次不高, 研究质量参差不齐, 甚至有些研究结果相悖^[69,70], 故需要更多实验证据以验证LIPUS治疗骨质疏松的有效性, 并完成体外实验到在体实

验, 最后到临床试验的过渡; (2) LIPUS治疗骨质疏松作用机制尚未明了, 超声生物效应对治疗效果具体有怎样的贡献, 仍然需要进一步探讨; (3) LIPUS刺激具体治疗参数的选择以及各参数之间如何组合才能达到最优化的治疗效果, 例如, 如何选择LIPUS刺激的强度、频率、占空比、持续时间等, 是目前研究最需要解决的关键问题; (4) 在选择最佳治疗参数组合的基础上, 研发便捷有效的LIPUS治疗骨质疏松的专用仪器也非常必要; (5) LIPUS治疗期限的选择以及其安全性的考虑, 也是学者们需要研究和探讨的重要课题。

相信随着对LIPUS与人体组织作用原理的认识不断加深, 超声波在骨科疾病中应用范围将越来越广泛, 甚至可以与其他治疗手段如药物等综合使用, 以期发挥更大疗效。

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Feasibility analysis of low-intensity pulsed ultrasound treatment for osteoporosis

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Osteoporosis is a musculoskeletal disease which is mainly characterized by bone loss and deterioration of bone microstructure, to which the middle-aged and elderly people are susceptible. It is often accompanied with bone pain, humpback, fractures and other symptoms, seriously affecting the quality of life of patients. As the population ages, osteoporosis incidence is increasing year by year, and currently these are approximately 200 million patients suffered from osteoporosis in the whole world. Furthermore, osteoporotic fracture has also caused great economic burden to families and society. On the other hand, in the weightless space environment, osteoporosis induced by unloading bones has become one of the important problems of astronauts' health, leading to impair their space exploration ability enhancement. Hence it is of great significance to its early diagnosis and timely treatment. Ultrasound as a therapeutic method has the advantage of low cost, non-invasive, non-ionizing radiation, fast and can be carried, and the findings in recent years show that ultrasonic backscatter signals can effectively reflect the micro-structure information of cancellous bone, therefore the evaluation of cancellous bone and diagnosis of osteoporosis with ultrasonic backscatter signal has become a focus. And clinical evaluation of bone has made significant progress in adults and newborns. Currently, the main treatment of osteoporosis is drug therapy (common used drugs are bisphosphonates, calcium, vitamin D, calcitonin, estrogen). Drug therapy typically has systemic effects along with side effects, however. Physical therapy such as ultrasound, magnetic therapy and hyperthermia is able to avoid the adverse effect of drug therapy. Low-intensity pulsed ultrasound (LIPUS) has been proved to be an effective mechanical signal to bone tissue and it is used to the treatment of orthopedic diseases, which can play its mechanical effect and avoid the damage of thermal effect to the tissue cells. Study in recent years has demonstrated that LIPUS with certain parameters plays a positive role in the progress of fracture healing, it can promote cell proliferation and differentiation, accelerate calcium mineralization and regulate gene expression and cell growth factors associated with bone tissue cells release, so as to accelerate the progress of bone formation and effectively shorten the healing time. Osteoporosis is a kind of bone disease with main feature of bone mass loss and it is reasonable to consider that the treatment of osteoporosis has the similar physiological mechanism as fracture healing, thus it may be an important potential means of osteoporosis treatment. By referring to numerous documentations related to "LIPUS", "fracture", "osteoporosis", this article begins from the bone structure and function, biological mechanisms of LIPUS treatment for orthopedic diseases and experimental methods of LIPUS treatment for osteoporosis to analyze and demonstrate the effective basis for LIPUS treatment of osteoporosis and review the current study situation of LIPUS treatment for osteoporosis, so as to provide theoretical evidences and new ideas for treatment of osteoporosis.

osteoporosis, low-intensity pulsed ultrasound (LIPUS), fracture, biological mechanisms

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