

·综述·

脊髓损伤后骨质疏松症的机制及治疗的研究进展

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近年来,随着社会经济的发展,脊髓损伤(spinal cord injury, SCI)发生率呈逐年增高的趋势,但其并发症并未得到有效的治疗,给患者家庭及社会带来巨大的负担。其中,骨质疏松症是SCI最常见的并发症之一,约有34.9%的SCI患者会出现骨质疏松症^[1],不仅加大了脊髓损伤患者的康复难度,还影响其后期的生存质量。SCI后骨质疏松症与普通骨质疏松发生机制有所不同,而且治疗手段有所差别。本文将对SCI后骨质疏松症的机制及治疗方法进行综述。

1 脊髓损伤后骨质疏松症的机制

1.1 机械刺激与负重对骨组织的影响

骨细胞能够感知骨骼上的机械刺激,通过细胞上的缝隙连接传递细胞内外的机械信号,然后将这些信号转化为生物反应,从而诱导成骨细胞成骨,并且抑制破骨细胞降解骨组织^[2]。SCI患者由于长期处于制动状态,缺乏机械刺激,易导致成骨细胞的形成受到抑制,破骨细胞吸收增加,最终导致骨丢失增加。同时,这种机械卸载的作用,主要影响到有负重倾向的皮下区域或骨小梁含量较高的区域,例如股骨远端和胫骨近端^[3]。Morse^[5]的动物实验证实,SCI损伤后的大鼠干骺端松质骨中骨细胞数量明显减少,成熟破骨细胞数量显著增加。同样也证实了SCI后会出现破骨细胞功能的增强,成骨细胞受到严重抑制,从而导致骨丢失。由此可知,SCI患者缺乏机械刺激容易导致骨丢失。

1.2 神经系统对骨组织的影响

P物质(SP)、降钙素基因相关肽(CGRP)、血管肠肽P(VIP)、神经肽Y(NPY)和酪氨酸羟化酶(TH)是在骨骼中检测到的神经肽,它们具有神经递质和免疫调节作用^[6]。Liu^[7]的动物研究发现SCI组大鼠与假手术组大鼠相比,损伤水平以下的骨骼中SP含量有所增加,他们还发现SP是通过促进RANKL/OPG的表达从而促进骨吸收,同时SP的高表达还导致SCI大鼠成骨作用受到抑制。同样地,Liu^[8]的试验也证实了SCI大鼠胫骨近端SP显著高于后肢固定大鼠,同时SCI大鼠SP免疫反应性神经纤维的神经支配密度显著增加,因此他们认为SP在SCI后骨质疏松症的发病机理中起重要作用。由此可知,SCI后患者由于骨骼中SP含量增高,打破了

成骨细胞的骨形成和破骨细胞的骨吸收平衡,从而导致骨丢失增多。

1.3 瘦素对骨组织的影响

瘦素是一种脂肪因子,主要通过中枢和外周途径调节骨形成和骨吸收。当瘦素被分泌到血液循环后,会跨越血脑屏障,与下丘脑上的受体结合后,信号通过交感系统传递给成骨细胞。它不仅可以增加RANKL受体的表达来抑制成骨细胞的增殖,还可以通过调节骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)促进脂肪生成,同时减少成骨^[9]。相反,中枢途径的瘦素可促进BMSCs增殖并向成骨细胞系分化,促进成骨细胞增殖,还可以通过降低RANKL受体激活剂的表达来抑制体外破骨细胞的生成^[10]。因此,瘦素本身可以根据信号通路对骨代谢产生相互竞争的影响。Sabour^[11]的研究证实了在SCI女性患者中,血清瘦素水平明显升高,骨密度明显降低。同时,Wang^[11]的动物研究也发现了SCI小鼠瘦素水平明显增高,但是骨密度是降低的。这证明了在SCI患者中,瘦素通过中枢途径抑制骨形成,促进骨吸收占更主要的作用。

1.4 甲状旁腺激素对骨组织的影响

急性SCI后,钙从骨骼中释放入血,钙离子水平明显升高。由于负反馈的机制 Ca^{2+} 会抑制甲状旁腺激素(parathyroid hormone, PTH)的释放。PTH水平降低会导致硬化素水平的增加^[13]。硬化素主要由骨细胞产生,它是通过抑制Wnt/ β -catenin信号抑制的骨形成和生长^[14]。Wnt与成骨细胞上的卷曲受体和LRP5/6的共同受体复合物结合,使 β -catenin移位到细胞核, β -catenin的转位促进了成骨细胞增殖^[15]。由此可知,PTH水平降低会导致骨形成受到抑制。Rivero^[16]的动物研究表明,SCI损伤1周后小鼠PTH水平没有显著下降,但是SCI损伤4周后小鼠血清PTH水平显著降低,同时小鼠后肢骨密度也显著降低。Sabour^[17]的研究虽然没有证实PTH水平降低与骨密度有显著的关系,但是他们仍然发现SCI患者PTH水平低于正常范围。因此,PTH水平降低可以引起SCI患者骨密度降低。

1.5 雌激素对骨组织的影响

研究已证明了SCI女性患者的下丘脑-垂体-卵巢轴出现

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异常,从而导致雌激素水平降低^[17]。雌激素可以抑制成骨细胞凋亡,同时也可通过抑制星形胶质细胞从而抑制NF- κ B,最终抑制破骨细胞分化^[19]。雌激素还会促进成骨细胞产生转化生长因子 β ,从而导致破骨细胞产生更多的Wnt,从而促进骨骼中的Wnt途径^[20]。Slade等^[20]在非卧床女性,绝经前SCI女性和绝经后SCI女性的研究中发现,SCI女性骨小梁的骨体积和骨小梁的骨间距明显下降,并且绝经后SCI女性比未绝经SCI女性骨小梁的骨体积和骨小梁的骨间距下降更明显。由此可知,SCI患者雌激素水平降低与骨丢失有关。同时,Gaspar AP^[22]发现了SCI患者的骨量与性激素有关。Jiang^[23]的动物实验也证实了SCI大鼠雌激素受体的下调与骨形成减少有关。因此,SCI对雌激素的抑制作用也是SCI所致骨质疏松症的发病机制。

1.6 胰岛素样生长因子对骨组织的影响

胰岛素样生长因子-I(insulin like growth factor-I, IGF-I)可以维持骨量,因此在骨骼生长过程中起着至关重要的作用^[23]。IGF-I是骨骼中含量最丰富的生长因子,在骨吸收过程中从骨基质中释放的IGF-1会产生成骨微环境,并诱导BMSCs分化,促进新骨形成^[25]。早在90年代初,Tsitouras^[26]已经证实了在SCI患者中,血清IGF-I的水平明显降低。同时,Jiang SD等^[27]将10只大鼠分为SCI组和假手术组,发现SCI组大鼠胫骨近端骨密度明显低于假手术组,同时IGF-I下降明显。此外,Allahdadi^[28]将IGF-1过度表达的BMSCs移植到SCI后的病变部位,发现IGF-1可以促进BMSCs在急性SCI中的骨再生。所以,SCI患者IGF-I水平下降也会导致骨质疏松症的发生。

2 脊髓损伤后骨质疏松症的治疗

2.1 药物治疗

骨质疏松症目前使用的药物包括:双膦酸盐、雌激素、核因子受体激活剂、抗硬化素抗体以及重组PTH1-34。双膦酸盐在急性和慢性SCI中都能减缓骨丢失,它是通过阻止破骨细胞附着到骨表面,抑制破骨细胞的骨吸收^[29]。对于患有SCI有绝经症状的女性,建议采用雌激素治疗预防骨质疏松症^[30]。核因子受体激活剂 κ B配体(RANKL)能刺激破骨细胞生成。与双膦酸盐相比,RANKL显著减少了侵蚀的骨表面^[31],这可能是急性SCI后药物疗效所必需的,因为急性SCI制动后不久就会出现骨吸收。抗硬化素抗体可以降低硬化素水平从而激活Wnt信号,使破骨细胞数量减少,成骨细胞数量增加^[32]。因此,抗硬化素抗体的处理可能是减少急、慢性SCI后骨丢失的一种高效药物。重组PTH1-34是目前唯一具有刺激成骨细胞活性和功能的药物,它是通过促进血管内皮细胞和BMSCs的增殖和分化,从而促进血管生成和成骨^[33]。但是持续给药明显延缓了骨痂的成熟和改建^[34]。

2.2 运动疗法

在急性和慢性SCI患者中进行运动疗法,可以实现负重减少导致骨量减少的逆转^[34]。Astorino^[36]的研究证实了运动疗法可以缓解骨密度的丢失。13例受试者接受了下肢活动治疗,分别在训练前后测量骨密度。6个月后发现脊柱骨密度有明显增加。近些年,Chain A等^[37]也做了类似的研究,他们发现体育锻炼可能有助于减轻脊髓损伤男性的股骨脱矿,并且越早开始锻炼,股骨骨密度就越高。Zhang^[38]使用幼鼠来研究不同强度的运动对骨量和骨强度的影响,他们发现中等水平的运动不仅能抑制骨吸收,促进骨量的增加,还可以促进成BMSCs水平增加。此外,运动过程中骨骼的机械负荷可能会逆转由于制动而导致的Wnt信号的改变,从而减少骨丢失。上述研究表明运动疗法是SCI后骨质疏松症的有效治疗手段,科学合理的运动训练能够提高骨分化能力,促进骨生成。

2.3 机械刺激疗法

低强度机械刺激(low-magnitude mechanical stimulation, LMMS)是全身振动(whole body vibration, WBV)疗法之一,它是将机械平台的马达产生的振荡能量传递到平台上的人体,从而产生类似负重锻炼的效果。因此,对骨质疏松症有很大的治疗潜力,可以改善骨形态,维持骨骼健康,而不会出现诸如颌骨坏死等药物的潜在副作用^[39]。LMMS可以促进成骨细胞增殖和细胞外基质矿化;同时可以诱导原代成骨细胞中细胞骨架排列的改善;还可以激活Wnt信号,使破骨细胞数量减少,成骨细胞数量增加^[40]。这种通过增加成骨细胞和减少破骨细胞的组合有助于骨形成和改善骨骼健康^[40]。Bodnyk KA^[39]将17只雌性小鼠分为LMMS组和假刺激组,两组都给予刺激8周,LMMS组在治疗8周后小鼠的骨骺骨形成率比假刺激组高。此外,Davis^[42]的个案研究中对一例SCI患者进行站立、部分站立以及结合振动的站立三个阶段治疗中发现,仅在结合振动的站立中SCI患者的骨密度显著增加。因此,对于SCI患者,LMMS可以作为一种减少骨丢失的潜在疗法^[42]。

2.4 功能性电刺激自行车运动

功能性电刺激疗法(functional electrical stimulation, FES)是通过表面电极的电刺激激活肌肉收缩,从而增加骨的密度和强度^[44]。同时,联合使用FES和站立的骨密度比单独使用FES有更明显的改善。因此,现如今功能性电刺激自行车(functional electrical stimulation cycling exercises, FES-CE)联合运动疗法较为多见。Lai CH^[45]的前瞻性研究的结果也表明FESCE可以减少骨丢失。他们把SCI患者分为FES-CE组和对照组,结果显示FESCE组治疗后股骨远端骨密度下降率明显低于对照组,但是停止治疗后,股骨远端骨丢失依旧会发生。此外,Johnston等^[46]还比较了两种不同模式

FESCE对骨密度的影响。他们把15例患者分为两组分别进行低频骑行与高频FES骑行治疗6个月,最终结果显示低频骑行获得了更大的改善。因此,FESCE治疗对SCI人群来说是非常重要的治疗手段。

2.5 超声疗法

超声(ultrasound,US)是一种以机械波形式传播的高频声能,它可以在特定区域施加局部机械刺激,机械刺激可以促进BMSCs的成骨分化^[46],从而有成骨效应。Kocyigit^[48]在新西兰兔进行低强度脉冲超声刺激(low intensity pulsed ultrasound stimulation,LIPUS),刺激前的骨密度作为基线,他们发现刺激30天和60天后的骨密度均高于基线,证实了超声波可以刺激骨生成。此外,He^[49]的研究也证实了超声波的成骨效应。他将BMSCs加入两种诱导剂诱导成骨细胞和血管内皮细胞,发现经过LIPUS的BMSCs表达了成骨细胞和血管内皮细胞分化标志物,并出现了早期成骨和血管生成,没有经过刺激的BMSCs成骨明显低于刺激组。因此,超声疗法可能是治疗SCI所致骨质疏松症的有效方法。

3 小结

SCI患者由于长期制动,缺乏机械刺激,从而使骨形成受到抑制,并间接刺激骨吸收。各种激素的调节失衡也可能在SCI引起的骨质疏松症中起作用,尽管需要更多的研究来建立这种关联。预防或治疗SCI引起的骨质疏松症的疗法包括抗硬化素抗体以及各种激素的替代疗法,还包括了使用ES或FES对下肢进行机械负荷,并通过振动疗法进行机械刺激以及超声疗法。然而,目前尚无标准的临床指南用于预防SCI后骨丢失。因此,我们在今后工作中应该为慢性SCI患者开发更多的治疗方法,从而为瘫痪的下肢提供足够的负荷,促进成骨,有效逆转SCI的骨质疏松症。

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