肠道菌群对肌骨健康的影响

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【摘要】 人体肠道菌群已被认为是调节宿主健康的重要因素之一,可参与体内多项生理过程,包括免疫反应、营养吸收、能量代谢、炎症反应、氧化应激和神经功能等。随着年龄的增长,宿主体内肠道菌群会发生显著变化,如菌群生物多样性降低、个体间组成差异升高以及病原微生物占比增高等,此类现象亦被证明与人体骨骼与肌肉组织发生退行性改变紧密相关。人体骨骼和肌肉组织对于维持身体机能以及提高生活质量具有重要意义,而骨骼肌肉系统退行性疾病是严重中老年人群生活质量并升高其他慢性疾病发病风险的重要原因之一。现有证据表明,肠道菌群因具有可改变、可重塑的特点,故可能是骨骼肌肉系统退行性疾病的潜在治疗靶点。本文对肠道菌群对骨骼和肌肉影响的研究进行综述,为领域内进一步开展相关研究、从调控肠道菌群角度改善人体肌骨健康提供参考。

【关键词】 肠道菌群;骨骼;肌肉

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Gut microbiota and musculoskeletal health

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【**Abstract**】 Human gut microbiota has been considered to be one of the important factors regulating host health. It can participate in a number of physiological processes in the body, including immune response, nutrient absorption, energy metabolism, inflammatory response, oxidative stress and neurological function. With aging, the gut microbiota in the host will change significantly, such as the decrease of microbial biodiversity, the increase of interindividual differences in composition, and the increase of the proportion of pathogenic microorganisms. These phenomena have also been shown to be closely related to the degenerative changes of human bone and muscle tissues. Human bone and muscle tissue play an important role in maintaining physical function and improving the quality of life. Musculoskeletal degenerative diseases are one of the important reasons for the quality of life of middle-aged and elderly people and increase the risk of other chronic diseases. Existing evidence shows that gut microbiota may be a potential therapeutic target for musculoskeletal degenerative diseases due to its modifiable and reshaping characteristics. Based on this, this article reviews the research on the effects of gut microbiota on bone and muscle, so as to provide a reference for further related research in the field and improve human muscle and bone health from the perspective of regulating gut microbiota.

【**Key words**】 Gut Microbiota; Skeleton; Muscle

人体骨骼和肌肉具有共同起源,均来自于胚胎时期中胚层组织,其中的成骨细胞和肌肉前体细胞逐渐发展成为骨骼系统和肌肉系统,共同为人体提供运动、支撑和保护功能[1,2]。维持良好的骨骼和肌肉健康对于保持身体机能以及提高生活质量具有重要意义。随着年龄的增长,骨骼肌肉系统会随之逐渐发生退行性改变,并成为中老年人疼痛的主要原因之一,可严重影响生活质量,并且可能升高其他慢性疾病的发病风险[3,4]。而随着人口老龄化程度不断增长,骨骼肌肉系统退行性疾病的发病率及患病率正在稳步上升[5,6]。因此,了解影响骨骼肌肉系统健康的重要因素,特别是可改变的影响因素,可能有助于提高生活质量、及时治疗疾病和预防继发慢性疾病[3,4,7]。最近逐渐受到关注的研究领域之一,即肠道菌群与衰老和骨骼肌肉系统有关,并被认为会影响骨骼和肌肉的健康。

人类肠道居住着数以万亿计的细菌,在成人体内以厚壁菌门(Firmicutes)和拟杆菌门(Bacteroidete)为主。它们与人体有着互惠的共生关系,对维持宿主健康至关重要[8]。研究发现,肠道菌群在胃肠道内可通过分解碳水化合物、蛋白质和脂质为宿主提供能量[9]。不仅如此,肠道菌群产物可以穿过肠道屏障或经其他器官进一步代谢进入循环系统,以调节胃肠道以外的其他重要组织或器官[10,11]。目前已有大量研究表明,肠道菌群可以通过“微生物-肠-骨轴”和“微生物-肠-肌轴”的双向交流机制来促进骨骼和肌肉生长并维持其健

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康[12~14]。然而,肠道菌群的多样性和丰度可随年龄增长而下降,生长环境、饮食营养等环境因素也可能会导致肠道菌群发生波动和改变,进而影响骨骼和肌肉组织的健康[15]。

本文旨在对既往肠道菌群与骨骼和肌肉相关的人群与基础研究进行综述,为领域内进一步开展相关研究,以及为从调控肠道菌群角度改善人体肌骨健康提供参考。

1 肠道菌群对骨骼的影响

成骨细胞和破骨细胞活性的平衡维持了机体骨形成和骨吸收之间的动态平衡,此重塑平衡被打破可导致多种骨骼疾病,包括骨质疏松症、骨关节炎等[16]。肠道菌群可能参与人体骨代谢调节,影响成骨细胞和破骨细胞的重塑平衡;而肠道菌群紊乱可能打破此平衡从而导致宿主骨质流失和骨质疏松[17],其研究发现,肠道菌群可能参与人体骨代谢调节,影响成骨细胞和破骨细胞的重塑平衡;而肠道菌群紊乱可能导致此平衡被打破以至于引起机体骨质疏松。目前,肠道菌群参与骨代谢的具体机制尚不明确。既往研究提示肠道菌群可能影响机体免疫细胞、钙吸收和内分泌系统从而调节骨代谢。例如,肠道菌群可激活宿主产生促炎或抗炎免疫反应,而免疫细胞通过表达大量细胞因子,继而直接或间接地通过促进破骨细胞生成来影响骨重塑,最终导致骨量减少[18]。研究发现,牙周炎大鼠补充鼠李糖乳杆菌(Lactobacillus rhamnosus)和长双歧杆菌(Bifidobacterium longum)后促炎细胞因子与核因子 κB 的表达降低,而抗炎细胞因子白介素-10 的表达增加,并表现为骨质流失减少,骨骼质量得到改善[19]。也有研究发现,肠道菌群产生的短链脂肪酸可以通过促进血清胰岛素样生长因子 1(一种已知可促进骨骼生长的激素)增加来间接促进骨量增加[20]。此外,短链脂肪酸也可通过诱导破骨细胞的代谢重编程并减少破骨细胞基因表达,从而抑制破骨细胞分化和骨吸收[21]。也有研究提示高胆固醇血症患者在补充罗伊氏乳杆菌(Lactobacillus reuteri)NCIMB 30242 后,血液中的 25-羟基维生素 D 水平显著升高,提示肠道菌群可能可以通过调节维生素 D 的代谢影响钙的吸收和利用来参与成骨过程[22]。

1.1 肠道菌群对骨骼影响的人群研究 研究发现,与骨密度正常人群相比,骨质疏松症患者肠道内 Actinomyces 菌属、Eggerthella 菌属、Clostridium Cluster XlVa 菌属、Lactobacillus 菌属、Blautia 菌属、Parabacteroides 菌属和 Ruminococcacee 菌属的相对丰度增加,表明这些菌属与骨密度呈负相关性[23, 24]。另一项研究利用来自弗雷明汉心脏研究和男性骨质疏松症研究的数据,发现梭状芽孢菌属 Clostridiales bacterium DTU089 丰度与胫骨骨密度呈负相关,Akkermansia 菌丰度与桡骨骨密度呈正相关,而 Lachnospiraceae NK4A136 和 Faecalibacterium 菌属丰度与胫骨骨密度呈正相关[25]。此外,既往研究发现骨质疏松症患者体内氧化三甲胺(Trimethylamine oxide, TMAO)水平升高,TMAO 是一种肠道菌群衍生的代谢物,已被证明可减少骨量生成[26]。一项病例对照研究发现,相比对照组,髋部骨折绝经后妇女的血清 TMAO 水平显著升高,提示血清 TMAO 水平升高可能与绝经后妇女骨质疏松症和骨折有关[27]。绝经后骨质疏松症患者表现出肠道菌群丰度和多样性显著降低[28~30]。也有研究发现,绝经后妇女的 Bacteroides 菌属丰度低与既往骨折史显著相关[31]。最近一项基于孟德尔随机化方法的全基因组关联研究确定了与骨量变异相关的 Clostridiales 菌属和 Lachnospiraceae 菌属,从基因层面提示肠道菌群与骨量之间存在因果关联[32]。

1.2 肠道菌群对骨骼影响的基础研究 已有研究发现新生无菌小鼠幼年期骨骼生长受到肠道菌群的影响。例如,与常规饲养的小鼠相比,无菌小鼠表现出了系列骨骼特征改变,如股骨长度缩短和皮质厚度变薄等[33]。相反,在成年动物模型中,与常规饲养的小鼠相比,广谱抗生素干预组小鼠骨量明显增加,具体表现为骨密度增加和破骨细胞数量减少[34]。研究发现给予成年无菌小鼠短期肠道菌群的定植后将引起骨吸收增加,进一步行长期定植也观察到了对骨形成代谢产生的积极影响,如纵向和径向骨生长增加等[20]。长期使用抗生素干预导致肠道菌群紊乱将使得小鼠骨组织强度受损,其中最为突出的是整个骨的弯曲强度降低[34];而在卵巢切除的 SD 大鼠试验中,补充益生菌将改善股骨的物理和生物力学性能[35]。亦有研究发现,对糖尿病雄性小鼠补充 Lactobacillus reuteri 菌可以有效地预防Ⅰ型糖尿病介导的骨量减少[36]。这些不同的结果提示,肠道菌群组成和定植时间会对不同小鼠的骨骼生长产生影响,动物年龄、动物品系和动物性别的差异也可能对既往肠道菌群与骨骼的研究结果产生影响。

2 肠道菌群对肌肉的影响

肠道菌群可能通过多种途径影响肌肉健康[37]。既往研究提示,肠道菌群可能通过对宿主代谢、免疫和神经系统发挥作用,调节肌纤维的大小和类型,从而影响肌肉含量、力量与功能[38~43]。肠道菌群失调可导致代谢紊乱和慢性炎症,进而引起宿主

肌肉含量减少和功能受损[15, 44]。而对宿主肠道菌群进行调控,有望改善宿主肌肉健康。例如,补充 Lactobacillus 菌属和 Bifidobacterium 菌属可显著提高老年小鼠的肌肉含量、力量和耐力[40]。定期补充益生菌也可显著提高老年人的肌肉质量和握力[45]。同时肠道菌群也可能降解老年小鼠的肌酸[46],而补充外源性肌酸可以逆转年龄相关的肌肉损失[47]。

2.1 肠道菌群对肌肉影响的人群研究 一项随机对照试验探讨了补充由菊粉和果聚糖的混合物组成的益生元产品对养老院入住老人虚弱状态的影响[48],结果发现,益生元干预组在接受 13 周持续干预后手握力得到显著改善。虽然这项研究未对受试者肠道菌群的组成进行具体评估,但益生元中包含的菊粉和果聚糖已被证实对人体肠道菌群存在有益影响[49, 50]。补充菊粉可以提高人类粪便中 Bifidobacterium 菌属、Anaerostipes 菌属和 Bilophila 菌属的相对丰度[51],而果聚糖可特异性地提高 Bifidobacterium 菌属的相对丰度[49, 50]。另一项观察性研究对 24 名酗酒者和 18 名对照者的肠道菌群组成进行了比较[52]。结果发现,与对照组相比酗酒者的手握力显著降低,同时肠道内 Proteobacteria 菌属、Sutterella 菌属、Clostridium 菌属和 Holdemania 菌属的相对丰度较高,而普氏粪杆菌菌种的相对丰度较低。不仅如此,该研究还探讨了受试者粪便中肠道菌群相关代谢物水平,发现酗酒者组粪便短链脂肪酸的水平降低,提示机体存在慢性炎症状态[52]。这些研究表明肠道菌群与肌肉力量之间存在一定关联。

蛋白质摄入已被证实可促进骨骼肌合成代谢继而使得机体肌肉质量增加,这一作用可能受肠道菌群所介导[53]。在一项对 38 例肥胖患者进行的随机对照试验中,使用酪蛋白和大豆蛋白,及作为对照的麦芽糊精试验者进行了为期三周的等热量补充[54],发现干预组患者肌肉质量有显著提高,蛋白质补充可使肠道菌群代谢明显转向氨基酸降解和发酵,提示肠道菌群可通过增加氨基酸的生物利用度来促进宿主体内的蛋白质合成。另有研究通过开展大规模粪便宏基因组测序,发现肌肉减少症患者与非肌肉减少症人群相比,肠道菌群的组成与丰度存在显著性改变,且肌肉减少症患者肠道内 Desulfovibrio piger 菌种、Clostridium symbiosum 菌种、Hungatella effluvii 菌种、Bacteroides fluxus 菌种、Absiella innocuum 菌种、Coprobacter secundus 菌种和 Clostridium citroniae 菌种的相对丰度显著上升,该研究提示这些菌种与肌肉减少症的患病存在显著正相关性[55]。

2.2 肠道菌群对肌肉影响的基础研究 既往研究发现,无菌小鼠即便在高脂肪饮食喂养下,仍表现出持续瘦表型[56]。然而,将营养不良患者的肠道菌群移植到无菌小鼠体内,即使在饮食营养均衡的情况下,也会导致小鼠骨骼肌生长障碍[57]。在高脂肪饮食小鼠中给予可产生短链脂肪酸的普氏粪杆菌会增加腓肠肌的肌肉含量,同时线粒体呼吸链复合体的表达也会增加[58]。也有研究发现,在高蛋白饮食喂食的小鼠中,肠道菌群中的 F/B 值(厚壁菌门与拟杆菌门相对丰度的比值)通常降低,有害菌占比通常增加,而产生如短链脂肪酸的代谢调节剂的肠道特定菌属明显减少,结果导致小鼠体重下降,可能对肌肉代谢产生了包括对炎症的调节作用减弱以及胰岛素抵抗增加的不利影响[59],提示从影响肠道菌群角度来看,高蛋白饮食并非总对肌肉有利。这些研究表明,肠道菌群可参与调节机体营养摄入,继而对肌肉合成或分解发挥作用[60]。此外,动物实验也证明了肠道菌群与肌肉之间存在紧密关联。例如,相比肌肉含量正常的大鼠,年龄相关性肌肉减少症大鼠模型的肠道菌群组成发生了显著改变,基因功能分析进一步提示肌肉减少症大鼠中参与碳水化合物、蛋白质、脂质消化和维生素生物合成的基因占比减少[38]。在小鼠肌少症模型中,移植 Lactobacillus reuteri 菌属会增加肌肉含量和肌纤维大小,该作用可能是通过上调 FoxN1 转录因子表达介导的抑制炎症所致[61]。也有研究发现,在白血病小鼠模型中,给予混合益生菌可显著降低肌萎缩蛋白等肌肉萎缩标志物的表达水平[62]。

3 小结

肠道菌群与宿主骨骼和肌肉健康之间存在紧密关联,鉴于肠道菌群具有可调控和可重塑的特点,进一步围绕肠道菌群与肌骨健康开展深入研究,以探讨肌骨系统疾病的肠源性发病机制以及潜在干预靶点具有重要意义。

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