doi: 10.13241/j.cnki.pmb.2022.07.007

海藻酸钙对骨质疏松症大鼠骨骼肌 SDF-1 含量和骨密度的影响 *

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摘要 目的:探讨海藻酸钙对骨质疏松症大鼠骨骼肌基质细胞衍生因子 -1(Stromal Cell-derived Factor-1,SDF-1)含量和骨密度的影响。**方法:**骨质疏松症大鼠(n=48)随机平分为三组 - 模型组、尼尔雌醇组与海藻酸钙组,在建模后 1 周后三组分别给予双蒸水、0.1 mg/100 g 尼尔雌醇与 37.5 mg/mL 海藻酸钙 / 枸杞多糖凝胶微球水溶液灌胃治疗,1 次 /d,检测大鼠骨骼肌 SDF-1 含量和骨密度变化情况。**结果:**(1)尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的血清钙离子含量高于模型组(P<0.05),磷离子含量低于模型组(P<0.05),尼尔雌醇组与海藻酸钙组对比差异有统计学意义(P<0.05);(2)尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的骨骼肌 SDF-1 含量低于模型组(P<0.05),海藻酸钙组低于尼尔雌醇组(P<0.05);(3)尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的腰椎和股骨骨密度高于模型组(P<0.05),海藻酸钙组低于尼尔雌醇组(P<0.05);(4)尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的股骨最大载荷、最大应力高于模型组(P<0.05),海藻酸钙组高于尼尔雌醇组(P<0.05);(5)海藻酸钙组造血细胞数量较多,骨皮质结构较完整,致密均匀粗壮,小梁数目明显增多,骨髓腔变小。**结论:**海藻酸钙在骨质疏松症大鼠的应用能抑制骨骼肌 SDF-1 的释放,有助于提高骨密度,改善骨生物力学指标,提高血清钙离子含量,降低磷离子含量。

关键词:海藻酸钙;枸杞多糖;骨质疏松症;大鼠;骨骼肌;基质细胞衍生因子 -1;骨密度
中图分类号:R-33;R68;R243 **文献标识码:**A **文章编号:**1673-6273(2022)07-1229-05

Effects of Calcium Alginate on SDF-1 Content and Bone Density of Skeletal Muscle in Rats with Osteoporosis*

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ABSTRACT Objective: To investigate the effects of calcium alginate on the content of skeletal muscle stromal cell-derived factor-1 (SDF-1) and bone density in rats with osteoporosis. **Methods:** Osteoporosis rats (n=48) were randomly divided into three groups-model group, nylestriol group and calcium alginate group. After modeling, the three groups were given double distilled water, 0.1 mg/ 100 g nilestriol, 37.5 mg/mL calcium alginate/Lycium barbarum polysaccharide gel microsphere aqueous solution were treated by intragastric administration, once a day, and the changes of SDF-1 content and bone density in rat skeletal muscle were detected. **Results:** (1) The serum calcium ion content of the nilestriol group and the calcium alginate group were higher than that of the model group at the 4th and 8th week of administration (P<0.05), and the phosphorus ion content were lower than that of the model group (P<0.05). There were statistically significant difference compared between the nylestriol group and the calcium alginate group (P<0.05). (2) The levels of SDF-1 in skeletal muscle of the nilestriol group and the calcium alginate group were lower than those of the model group at the 4th and 8th week of administration (P<0.05), and the calcium alginate group were lower than that of the nilestriol group (P<0.05). (3) The bone mineral density of the lumbar spine and femur in the nilestriol group and the calcium alginate group were higher than that of the model group at the 4th and 8th week of administration(P<0.05), and the calcium alginate group were lower than that of the nilestriol group (P<0.05). (4) The maximum load and maximum stress of the femur in the nilestriol group and the calcium alginate group were higher than that of the model group at the 4th and 8th week of administration (P<0.05), and the calcium alginate group were higher than that of the nilestriol group (P<0.05). (5) The number of hematopoietic cells in the calcium alginate group were larger, the cortical bone structure were relatively complete, dense and uniform, the number of trabeculae increased significantly, and the bone marrow cavity became smaller. **Conclusion:** The application of calcium alginate in osteoporotic rats can inhibit the release of SDF-1 in skeletal muscle, increase bone density, improve bone biomechanical indexes, increase serum calcium ion content, and reduce phosphorus ion content.

Key words: Calcium alginate; Wolfberry polysaccharide; Osteoporosis; Rat; Skeletal muscle; Stromal cell-derived factor-1; Bone mineral density

* 基金项目:陕西省自然科学基础研究计划项目(2021JQ-925)
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(收稿日期:2021-08-04 接受日期:2021-08-31)

Chinese Library Classification(CLC): R-33; R68; R243 Document code: A
Article ID:1673-6273(2022)07-1229-05

前言

骨质疏松症(Osteoporosis,OP)是中老年人群中最常见的疾病之一,其以骨量减少、骨组织微结构退化为主要特征的骨代谢性疾病[1]。骨质疏松症最常见的并发症是骨折,特别是很多患者尤其是女性患者伴随有雌激素水平下降和破骨细胞活性增高,使其骨吸收超过骨形成而导致骨丢失,其中以脊椎骨丢失最为明显[2,3]。当前对于骨质疏松症尚无特效治疗方法,多数患者需长期服用雌激素替代药物,不过长期服用上述药物容易出现一些不良反应,甚或增加机体发生乳腺癌和子宫内膜癌的几率[4,5]。现代中医发现多种植物提取物具有拟雌激素样作用,可以起到防止骨丢失、减少骨吸收等作用[6]。枸杞多糖属于植物雌激素,具有抑制破骨细胞性骨吸收和分化,促进成骨细胞增殖、分化和矿化,增加骨密度等多种作用[7,8]。海藻酸钙(Calcium alginate,ALG-Ca)具有价格便宜、容易获得、生物相容性好、降解性强等优点,当前与枸杞多糖可联合使用于药物缓释中[9,10]。SDF-1 是一种具有趋化活性的细胞因子,属于巨噬细胞内分泌型炎性蛋白超家族成员,在多种骨科疾病的发生发展中起重要作用[11,12]。但当前暂无关于海藻酸钙与 SDF-1 的研究。本文创新性的探讨了海藻酸钙对骨质疏松症大鼠骨骼肌 SDF-1 含量和骨密度的影响,以明确海藻酸钙的作用效果与机制。

1 材料与方法

1.1 研究材料

SPF 级 8 周龄雌性 SD 大鼠购自北京维通利华实验动物技术有限公司(n=52,体重 220±20 g,批号 281100032),饲养于本院实验动物中心,严格按照动物伦理标准进行实验操作,饲养环境通风良好,湿度、温度恒定,自由饮水摄食。海藻酸钙 / 枸杞多糖凝胶微球购自西安开来生物工程有限公司(批号 2877221,纯度≧70.0%),尼尔雌醇(国药准字 H11020123,廊坊高博京邦制药有限公司),SDF-1 检测试剂盒购自武汉博士德公司,血清钙离子、磷离子检测试剂盒购自美国 Sigma 公司,骨生物力学实验机购于美国 MA 公司(MTS-858 型),双能 X 射线骨密度检测仪购于美国 GE 公司(LunariDXA 型)。

1.2 骨质疏松症大鼠模型的建立

所有大鼠都给予经腹腔行双侧卵巢切除术,以此建立骨质疏松症模型。建模过程:所有手术器械高温消毒,大鼠给予 10 % 水合氯醛 0.3 mL/100 g 腹腔注射麻醉,于腹正中线切开皮肤,分离皮下组织及肌肉筋膜进入腹腔,找到卵巢后,结扎并切除双侧卵巢,缝合肌肉与皮肤,明胶海绵止血,预防术口感染,放回饲养笼中,注意保暖。

1.3 大鼠分组与治疗

将建模成功的大鼠(n=48)随机平分为三组 - 模型组、尼尔雌醇组与海藻酸钙组,在建模后 1 周后三组分别给予双蒸水、0.1 mg/100 g 尼尔雌醇与 37.5 mg/mL 海藻酸钙 / 枸杞多糖凝胶微球水溶液灌胃治疗,1 次 /d,持续给药,在给药第 4 周与第 8 周三组分别各处死 8 只大鼠进行后续实验。

1.4 观察指标

(1)采用急性大失血法处死大鼠,抽取腹主动脉 4-5 mL,3000 r/min 离心 10 min,收集上层血清,采用原子光谱法检测血清钙离子、磷离子含量。(2)取大鼠的右后肢股骨和左后肢腓肠肌白肌部分,剪刀剪碎后进行研磨,以 3000 r/min 离心 15 min,取上层骨骼肌组织,采用酶联免疫法检测骨骼肌 SDF-1 水平。(3)取大鼠 L4 腰椎和右股骨,采用双能 X 射线骨密度检测仪检测骨密度值。(4)取出右侧股骨,将置于生物力学材料试验机进行三点弯曲力学试验,记录股骨最大载荷、最大应力。(5)取 L4 椎体 10 %甲醛溶液固定,脱钙后制备石蜡切片,采用 HE 染色观察骨组织病理学形态变化。

1.5 统计学处理

本研究所有实验数据结果采用 SPSS 21.00 统计软件进行处理,均行正态性、方差齐性检验,两两对比为 SNK-q 检验,多组间对比为单因素方差分析法,检验水准为 α=0.05。

2 结果

2.1 血清钙离子、磷离子含量对比

尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的血清钙离子含量高于模型组 (P<0.05),磷离子含量低于模型组(P<0.05),尼尔雌醇组与海藻酸钙组对比差异有统计学意义(P<0.05)。见表 1。

表 1 三组给药不同时间点的血清钙离子、磷离子含量对比(mmol/L,均数±标准差)

Table 1 Comparison of serum calcium and phosphorus ions in different time points (mmol/L, mean±standard deviation)

Groups	n	Calcium ions		Phosphorus ion	
		4 weeks of dosing	8 weeks of dosing	4 weeks of dosing	8 weeks of dosing
Calcium alginate group	8	2.33±0.13*#	2.35±0.13*#	1.67±0.22*#	1.68±0.18*#
Neil estradiol group	8	2.21±0.21*	2.26±0.12*	1.76±0.13*	1.78±0.14*
Model Group	8	2.09±0.22	2.10±0.18	1.93±0.16	1.94±0.20

Note: Compared with the model group, *P<0.05; compared with the Nilestriol group, #P<0.05.

2.2 骨骼肌 SDF-1 含量对比

尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的骨骼肌 SDF-1 含量低于模型组(P<0.05),海藻酸钙组低于尼尔雌醇组(P<0.05)。见表 2。

2.3 骨密度对比

尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的腰椎和

股骨骨密度高于模型组(P<0.05),海藻酸钙组低于尼尔雌醇组 (P<0.05)。见表 3。

表 2 三组给药不同时间点的骨骼肌 SDF-1 含量对比(pg/mL,均数± 标准差)

Table 2 Comparison of skeletal muscle SDF-1 at different points of administration (pg/ml, mean± standard deviation)

Groups	n	4 weeks of dosing	8 weeks of dosing
Calcium alginate group	8	133.52±9.24*#	111.37±12.57*#
Neil estradiol group	8	167.98±12.47*	133.28±14.92*
Model Group	8	213.25±13.29	214.02±15.62

Note: Compared with the model group, *P<0.05; compared with the Nilestriol group, #P<0.05.

表 3 三组给药不同时间点的骨密度对比(g/cm^2,均数±标准差)

Table 3 Bone density comparison at different points of administration (g/cm^2, mean ± standard deviation)

Groups	n	Lumbar spine		Femur bone	
		4 weeks of dosing	8 weeks of dosing	4 weeks of dosing	8 weeks of dosing
Calcium alginate group	8	0.30±0.03*#	0.33±0.05*#	0.21±0.03*#	0.24±0.03*#
Neil estradiol group	8	0.24±0.04*	0.25±0.04*	0.19±0.02*	0.20±0.04*
Model Group	8	0.22±0.03	0.21±0.04	0.17±0.02	0.17±0.03

Note: Compared with the model group, *P<0.05; compared with the Nilestriol group, #P<0.05.

2.4 骨生物力学指标对比

尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的股骨最大载荷、最大应力高于模型组(P<0.05),海藻酸钙组高于尼尔雌醇组(P<0.05)。见表 4。

表 4 三组给药不同时间点的股骨生物力学指标对比(均数±标准差)

Table 4 Comparison of femoral biomechanical indexes of different time points of three groups(mean±standard deviation)

Groups	n	Maximum load (N)		Maximum stress (Mpa)	
		4 weeks of dosing	8 weeks of dosing	4 weeks of dosing	8 weeks of dosing
Calcium alginate group	8	165.22±13.11*#	169.33±12.57*#	180.44±12.70*#	183.76±11.46*#
Neil estradiol group	8	124.87±16.38*	131.47±13.00*	143.82±13.33*	158.76±13.87*
Model Group	8	106.25±15.28	106.81±16.33	134.33±18.02	134.87±17.33
F		32.374	40.091	21.439	22.986
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the Nilestriol group, #P<0.05.

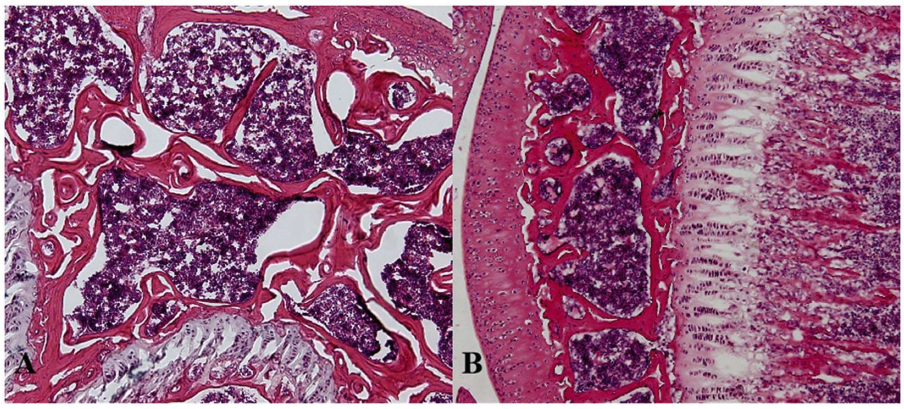

图 1 模型组和尼尔雌醇组骨组织病理学染色结果(A:模型组,B:尼尔雌醇组;10×)

Fig.1 Bone histopathological staining results of model group and nilestriol group (A: model group, B: nilestriol group; 10×)

2.5 病理特征对比

模型组:骨皮质明显变薄,空泡样脂肪细胞增多,髓腔扩大,骨小梁稀疏纤细或断裂。尼尔雌醇组:造血细胞数量增多,骨皮质变厚,骨小梁数量稍增多,骨髓腔稍小。海藻酸钙组:造血细胞数量较多,骨皮质结构较完整,致密均匀粗壮,小梁数目明显增多,骨髓腔变小。

3 讨论

骨质疏松症是一种全身代谢性骨病，在全球具有极高的发病率、致死率，且其相关医疗费用耗费巨大，对患者家庭造成一定的经济压力。随着经济社会的快速发展、生活工作节奏的加速以及人类平均寿命延长，当前骨质疏松症的发病率逐年提高[13]。该病为一种进行型骨骼系统疾病，病理特征为骨密度降低和骨组织微结构的改变，具有骨折率高、致残率高等特点，对患者健康产生了极大的影响，严重影响其生活质量[14]。骨质疏松症治疗方法包括激素替代、中药、针灸等，但补充雌激素是当前多数中老年骨质疏松症患者的治疗方法，该方法能够改善患者对肌体高转换型骨代谢的不利影响，缓解骨质疏松症状，但因长期使用雌激素会出现较多的不良反应[15]。

枸杞多糖为枸杞的主要成分之一，具有调节免疫力、抗骨质疏松、延缓衰老等多种作用，能提高去势雌性大鼠血清中的一氧化氮水平，从而降低大鼠骨胶原的代谢水平，抑制其骨代谢的高转换状态。海藻酸钙来源广泛，其结构中的 G 单元能与镁离子、铝离子等多种二、三价金属离子形成螯合结构，并且能作为注射支架材料用于软骨组织再生等[16]。相关研究显示：枸杞多糖与海藻酸钙复合使用，不仅可以保护枸杞多糖，而且可以延长枸杞多糖在胃肠道吸收时间，从而中骨质疏松治疗中具有促进骨再生的作用[17,18]。本研究经分析三组血清钙离子、磷离子含量发现，尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的血清钙离子含量、腰椎和股骨骨密度高于模型组，磷离子含量低于模型组，表明海藻酸钙在骨质疏松症大鼠的应用能提高骨密度与血清钙离子含量，降低磷离子含量，从而对骨质疏松产生积极作用，与上述研究[17,18]结论一致。

SDF-1 是一种强佑林的趋化因子，从骨髓基质细胞分离出来的 CXC 类趋化蛋白，在肾脏、心脏、骨及牙齿等损伤或者缺损部位均有所表达。SDF-1 与 CXCR4 结合后可作用于下游信号通路，从而参与机体器官发育、白细胞浸润、炎症反应等过程[19,20]。SDF-1 含量的增加可激活 CXCR4 信号，以此促进破骨细胞的增殖。而抑制 SDF-1/CXCR4 信号通路的激活能减缓软骨退化，也能预防创伤后骨关节炎骨小梁丢失[21,22]。经对比三组的骨骼肌 SDF-1 含量可知，尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的骨骼肌 SDF-1 含量低于模型组，海藻酸钙组低于尼尔雌醇组，结合 Fragkiadaki P 等[23]研究分析其原因在于：海藻酸钙 / 枸杞多糖能够促进成骨细胞的增殖、分化及矿化功能，增加骨量骨强度，从而改善骨结构，最终促进骨形成。另外，Fuggle NR[24]和 Galindo-Zavala R[25]的研究发现：枸杞多糖可作用于骨细胞雌激素受体，发挥雌激素样生理效应，调节骨代谢；而海藻酸钙凝胶微球具有生物相容性、可降解性等优点，同时具备调节免疫功能、抑制炎症等功能，可持续发挥降低 SDF-1 表达的作用，进而提高骨密度，与本研究结果一致。

摘除卵巢后的大鼠可随着雌激素减少出现骨的形成与吸收失衡，当前在临床上多应用于建立骨质疏松症模型[26,27]。本研究显示在骨组织病理染色中，模型组大鼠摘除卵巢后，骨小梁变薄，出现连续性中断、间隙变大，证明大鼠骨质疏松模型制备成功。同时骨生物力学指标对比结果显示，尼尔雌醇组与海藻酸钙组给药第 4 周与第 8 周的股骨最大载荷、最大应力高于模型组，海藻酸钙组高于尼尔雌醇组，结合 Keaveny TM [28]和 Kendler DL[29]的研究内容分析：枸杞多糖可刺激破骨细胞内的凋亡活性增加，进而使骨形成大于骨破坏，从而有利于改善机体的骨生物力学作用。另外，相关研究显示：海藻酸钙凝胶微球具有良好的生物相容性，实验结果中发现未见明显的刺激与炎症反应，能够在组织中起到良好的药物载体作用，可稳定血药浓度，从而持续改善骨质疏松的生物学效应[30,31]。本研究也存在一定的不足，没有进行其他药物的相关机制分析，也没有设置空白对照组排除其他干扰因素，以及没有进行体外机制分析，将在后续研究中继续进行深入的探讨。

综上所述，海藻酸钙在骨质疏松症大鼠的应用能显著抑制骨骼肌 SDF-1 的释放，提高骨密度，改善骨生物力学指标，提高血清钙离子含量，降低磷离子含量，为临床治疗应用提供一定的理论基础。

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（上接第 1228 页）

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