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·论著·

口服淫羊藿苷可提高大鼠的峰值骨密度和骨质量

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摘要:**目的** 研究口服淫羊藿苷(Icariin, ICA)是否能提高大鼠的峰值骨密度和骨质量,起到预防骨质疏松症的作用。**方法** 1 月龄雌性健康 SD 大鼠随机分为两组,每组 12 只。服药组每日灌服 25 mg/kg 淫羊藿苷,对照组(CON)灌服给予等体积蒸馏水。每周监测大鼠体重。每月检测实验鼠的骨密度,3 个月后处死所有大鼠。取血测血清骨钙素(OC)和抗酒石酸性磷酸酶 5b(TRACP 5b)的含量。取双侧股骨和胫骨分别进行骨密度检测、μCT 扫描和生物力学评价。剥离心、肝、胃、肾、肾上腺和子宫后称重,计算器官指数,并做常规病理学检测。**结果** 两组大鼠的体重始终无显著性差异($P>0.05$);各脏器的器官指数均无明显差异,病理学观察未见异常改变。第 1、第 2 月的全身骨密度无明显差别($P>0.05$),但 3 个月后,ICA 组显著高于 CON 组,股骨骨密度存在相同趋势($P<0.05$);ICA 组的血清 OC 水平升高,而 TRACP 5b 含量下降($P<0.05$);μCT 检测结果是:ICA 组的骨体积百分率、骨小梁厚度和骨小梁数量均高于 CON 组,但骨小梁分离度和模型系数显著低于 CON 组($P<0.05$);股骨最大载荷、弹性模量和屈服强度均是 ICA 组显著高于 CON 组($P<0.05$)。**结论** 口服淫羊藿苷可通过抑制骨吸收而促进骨形成,提高大鼠的峰值骨密度和骨质量,对预防各种原因引起的骨质疏松及骨质疏松性骨折具有十分重要的意义。

关键词:淫羊藿苷;骨密度;骨质量;生物力学;骨组织微结构

Oral medication of icariin enhances peak bone mineral density and bone quality in rats

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Abstract: **Objective** To investigate the effect of the oral medication of icariin (ICA) on bone mineral density (BMD) and bone quality in rats. **Methods** Twenty-four 1-month-old female SD rats were randomly divided into 2 groups, and each group had 12 rats. Rats in the medication group were given an oral administration of 25mg/kg icariin, while rats in control group (CON) were given an administration of same volume of distilled water. The body weight of all the rats was monitored weekly. And BMD of all the rats was measured monthly. All the rats were sacrificed after 3-month treatment. Blood was collected and the serum levels of osteocalcin (OC) and anti-tartaric acid phosphatase 5b (TRACP 5b) were measured. The bilateral femurs and the tibia were also collected and BMD detection, μCT scanning, and biomechanical evaluation were performed. The heart, the liver, the stomach, the kidney, the adrenal, and the uterus were all collected and weighted. The organ index was calculated and the routine pathological detection was performed. **Results** No significant difference of the body weight of the rats in both groups was observed during 3 months ($P>0.05$). The organ index of all the organs showed no significant difference, and the pathological observation also showed no abnormal changes. BMD of the total bone in both groups at the 1st and the 2nd month showed no significant difference ($P>0.05$), but 3 months later, BMD in ICA group was significantly higher than that in CON group, and the same trend was also observed in the BMD of the femur ($P<0.05$). The serum level of OC in ICA group increased while the level of TRACP 5b decreased ($P<0.05$). The result of μCT scanning revealed that the bone volume/tissue volume, the trabecular thickness, and the trabecular number in ICA group were all higher than that in CON group, but the trabecular separation and the coefficient of the model were significant lower than that in CON group ($P<0.05$). The maximum load, the elasticity modulus, and structural model

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index (SMI) of the femur in ICA group were significantly higher than that in CON group ($P < 0.05$). **Conclusion** Oral medication of icariin can promote bone formation by inhibiting bone resorption, improve peak BMD and bone quality, which has significant importance for the prevention of osteoporosis and osteoporotic fractures caused by different reasons.

Key words: Icariin; Bone mineral density; Bone quality; Biomechanics; Bone microarchitecture

骨质疏松症是一种普遍随年龄增长而形成的骨和矿物紊乱的疾病[1]。骨质疏松症是由峰值骨量和年龄增长相关的骨丢失两方面决定的[2]。峰值骨量(PBM) 是骨成熟末期达到的最大骨量,是骨最坚硬和骨矿含量最高的时期[3]。高 PBM 会在一定程度上减缓发病的机率[4]。因此,提高 PBM 是一条预防骨质疏松的理想途径。淫羊藿具有强筋健骨之功效,常用于治疗骨质疏松或促进骨折愈合[5]。ICA 是淫羊藿中含量最为丰富的黄酮苷类化合物,我们前期的研究表明,ICA 可抑制体外培养破骨细胞骨吸收活性,促进骨髓基质细胞增殖和向成骨性分化,同时能促进成骨细胞的分化和成熟[6-8],因而推测其可能具有抗骨质疏松活性。本实验考察了口服淫羊藿苷对大鼠峰值骨密度和骨质量的影响,以期对其抗骨质疏松活性作出初步判断。

据 Bhargavan 等[9]报道,通过口服 Medicarpin 提高峰值骨量可达到预防骨质疏松症的目的。

1 材料和方法

1.1 实验动物

1 月龄 SD 雌性大鼠 24 只,SPF 级,体重(125 ± 3)g,由甘肃省中医学院实验动物中心提供(合格证号:SCXK (甘) 2004-0006-152);淫羊藿苷购自陕西宝鸡辰光生物科技有限公司,纯度≥98%;双能 X 射线骨密度仪(GE 公司,美国)、μCT (MILabs 公司,荷兰)和 AG-IS 万能材料试验机(岛津公司,日本)均为本实验室仪器;抗酒石酸酸性磷酸酶试剂盒和骨钙素试剂盒为英国 IDS 公司产品。

1.2 实验设计

1 月龄 SD 雌性大鼠随机分为两组,每组 12 只,一组每日灌服(ig)淫羊藿苷,称为服药组,另一组只给予等体积蒸馏水,用作对照组。淫羊藿苷用蒸馏水配成 2.5 mg/mL 的混悬液。按每只大鼠 25 mg/kg 体重给药。大鼠饲养于 SPF 级实验室,自由摄水和进食,记录每日进食量和进水量,每周称 1 次体重。动物处死后迅即剥离出心、肝、胃、肾、肾上腺和子宫,称重,计算器官指数,并将所有器官固定于 10% 福尔马林中,石蜡包埋,常规切片,HE 染色,由高年资深病理医师进行病理学观察与评价。

1.3 检测项目

1.3.1 骨密度的测定:每月在麻醉状态下测 1 次全身骨密度,第 3 个月测完后即处死所有动物,剥离出四肢长骨,左侧股骨用于检测骨密度。麻醉采用 10% 水合氯醛,剂量为 3 mL/kg,腹腔注射(ip)。

1.3.2 血清生化指标的测定:采用心脏取血法抽取血样,3000 r/min,5 min 离心,取上层血清, -80℃保存;按试剂盒说明书制作 OC 和 TRACP 5b 标准曲线,OC 于 450 nm、TRACP 5b 于 405 nm 处测定 OD 值,通过标准曲线计算出含量。

1.3.3 μCT 影像分析:将右侧股骨用 70% 酒精固定。感兴趣区域选择在距生长板 1 mm 位置。分析参数包括相对骨体积率(bone volume/tissue volume, BV/TV)、骨小梁厚度(trabecular thickness, Tb.Th)、骨小梁数量(trabecular number, Tb.N)、骨小梁分离度(trabecular spacing, Tb/Sp)和模型系数(structural model index, SMI),并采集成像图片。

1.3.4 生物力学分析:将左侧股骨用浸透 0.9% 生理盐水的纱布包裹后保存于 -20℃。在实验 24 h 前取出,于室温下自然解冻。三点弯曲试验的跨距为 17 mm,速度为 10 mm/min。记录载荷变形曲线,得到,包括最大载荷、屈服强度和弹性模量等指标。

1.4 统计学处理

统计分析均采用 SPSS16.0(SPSS 公司,美国)软件完成,所有检测数据表示均用均数 ± 标准差,用 t 检验作显著性分析。以 $P < 0.05$ 为显著性差异,$P < 0.01$ 为极显著性差异。

2 结果

2.1 对进食量、进水量、体重和脏器病理学的影响

两组大鼠的每日进食量和进水量始终无明显差别,体重虽然随时间增长而增加,但也未出现显著性差异(图 1),表明灌服淫羊藿苷对饮食和体重均无影响。各器官指数无显著差异($P > 0.05$);病理学观察也未见异常改变。

2.2 对大鼠骨密度的影响

两组大鼠的全身骨密度在实验开始时(TBMD-MO)、服药 1 月后(TBMD-M1)和服药 2 月后(TBMD-M2)均无明显差别(表 1),但 3 个月后

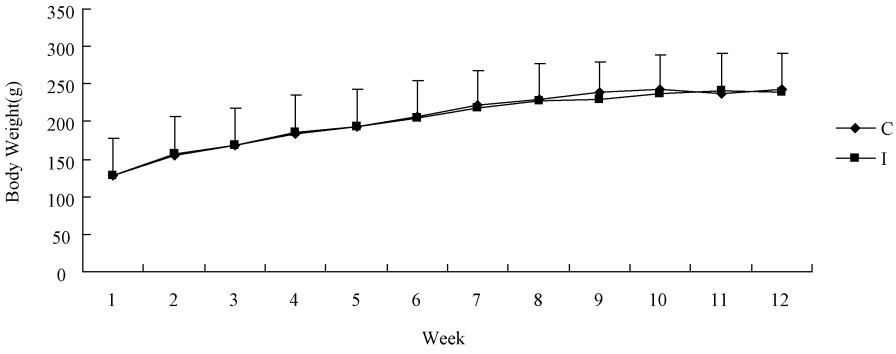

图 1 大鼠体重的变化曲线

图中 C 为对照组,I 为 ICA 组

Fig. 1 The changing curve of the body weight of rats

C: control group; I: ICA group

(TBMD-M3)出现极显著性差异($P < 0.01$)。动物处死后离体检测股骨骨密度的结果也出现相同趋势(表 1),表明连续口服淫羊藿苷三个月后大鼠骨密度较未服药者有明显提高。

表 1 不同时间大鼠全身骨密度和股骨骨密度检测结果(g/cm^3, $\bar{x} \pm s$, $n = 12$)

Table 1 Results of BMD of the total body and the femur of rats at different time points (g/cm^3, $\bar{x} \pm s$, $n = 12$)

Group	TBMD-M0	TBMD-M1	TBMD-M2	TBMD-M3	FBMD-M3
CON	0.112 ± 0.006	0.140 ± 0.007	0.151 ± 0.008	0.148 ± 0.01	0.144 ± 0.006
ICA	0.111 ± 0.006	0.144 ± 0.007	0.153 ± 0.009	0.160 ± 0.01 **	0.154 ± 0.009 **

注:与对照组组相比, ** 表示 $P < 0.01$;

TBMD-M0:开始服药前全身骨密度;TBMD-M1:服药 1 个月后骨密度;TBMD-M2:服药 2 个月后全身骨密度;TBMD-M3:服药 3 个月后骨密度;FBMD-M3:服药 3 个月后股骨骨密度

TBMD-M0: basal total BMD; TBMD-M1: BMD after experiment 1 month; TBMD-M2: basal total BMD; TBMD-M3: BMD after experiment 1 month; FBMD-M3: femur BMD after experiment 3 month

2.3 对大鼠血清 OC 和 TRACP 5b 含量的影响

OC 由成骨细胞分泌,是骨形成特异性指标,TRACP 5b 由破骨细胞分泌,是骨吸收特异性指标。如表 2 所示,ICA 组大鼠的血清 OC 水平极显著高于对照组($P < 0.01$),而血清 TRACP 5b 水平显著低于对照组($P < 0.05$),说明口服淫羊藿苷 3 个月后,大鼠体内骨形成水平提高,同时骨吸收活动减弱。

表 2 大鼠血清 OC 和 TRACP 5b 的含量($\bar{x} \pm s$, $n = 12$)

Table 2 Serum levels of OC and TRACP 5b in rats ($\bar{x} \pm s$, $n = 12$)

Group	OC (ng/mL)	TRACP (U/L)
CON	72.793 ± 1.554	0.731 ± 0.181
ICA	74.91 ± 1.337 **	0.593 ± 0.077 *

注:与对照组相比, ** 为 $P < 0.05$, * 为 $P < 0.01$。

OC:骨钙素;TRAP5b:抗酒石酸性磷酸酶 5b

OC: osteocalcin; TRACP 5b: anti-tartaric acid phosphatase 5b

2.4 μ CT 影像分析结果

如表 3 所示,ICA 组骨体积百分率(BV/TV)、骨

表 3 ICA 对大鼠股骨 micro-CT 分析的影响($\bar{x} \pm s$, $n = 5$)

Table 3 Effect of ICA on the micro-CT analysis of the rat femur ($\bar{x} \pm s$, $n = 5$)

Group	BV/TV(%)	TB.N(/mm)	TB.TH(mm)	TB.SP(mm)	SMI(-)
CON	31.898 ± 1.486	2.419 ± 0.091	0.132 ± 0.001	0.433 ± 0.084	0.920 ± 0.190
ICA	45.263 ± 6.06 *	3.012 ± 0.173 **	0.152 ± 0.010 *	0.249 ± 0.045 *	0.347 ± 0.233 *

注:与对照组相比, * 为 $P < 0.05$, ** 为 $P < 0.01$;

BV/TV:相对骨体积;TB.N:骨小梁数量;TB.TH:骨小梁厚度;

TB.SP:骨小梁分离度;SMI:模型系数;

BV/TV: bone volume/tissue volume; TB.N: trabecular thickness;

Tb.Th: trabecular number; Tb/Sp: trabecular spacing; SMI: structural model index

小梁数(TB. N)和骨小梁厚度(TB. TH)明显高于 CON 组($P<0.05$),但骨小梁分离度(TB. SP)和模型系数(SMI)明显低于 CON 组($P<0.05$),说明口服淫羊藿苷 3 个月后骨组织微结构明显优于对照组(图 2)。

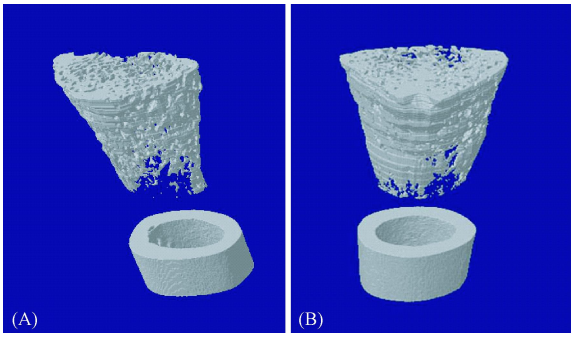

图 2 大鼠股骨 micro-CT 成像分析三维图片

(A)为对照组,(B)为 ICA 组。

Fig. 2 Three-dimensional reconstruction of the femur micro-CT of rats

(A): control group; (B): icariin group

2.5 对大鼠骨生物力学的影响

如表 4 所示,股骨三点弯曲实验发现,ICA 组的最大载荷和屈服强度极显著高于 CON 组($P<0.01$),弹性模量显著高于 CON 组($P<0.05$),表明口服淫羊藿苷 3 个月后骨生物力学指标全面提高。

表 4 ICA 对大鼠骨生物力学的影响($\bar{x}\pm s, n=12$)

Table 4 Effect of ICA on bone biomechanics in rats ($\bar{x}\pm s, n=12$)

Group	最大载荷(N)	弹性模量(mPa)	屈服强度(N)
CON	125.0 ± 17.7	1526.2 ± 247.3	114.2 ± 14.5
ICA	156.2 ± 14.3 **	2288.5 ± 305.8 **	138.2 ± 30.4 *

注:与对照组相比,* 为 $P<0.05$,** 为 $P<0.01$

3 讨论

峰值骨密度是指人一生发育过程中骨形成与骨吸收达到平衡状态时的骨密度,此前骨形成活跃程度高于骨吸收,是骨量积累的关键时期[10]。所以选择刚断乳 1 月龄大鼠开始给药,以便系统考察口服淫羊藿苷对大鼠峰值骨量的影响。由于是否发生骨质疏松性骨折是由骨强度而非单纯骨密度决定的,骨强度包括骨密度和骨质量两部分内容[11,12],我们还采用 μCT 和生物力学试验评价了口服淫羊藿苷对骨质量的影响。

实验过程中,实验组大鼠的进食量、进水量和体重与对照组无显著性差异。心、肝、脾、肾、肾上腺、胃和子宫湿重和器官系数均无明显差别,病理学观察也未见异常变化。表明口服淫羊藿苷 3 个月对大鼠饮食无不良影响。但全身骨密度在服药 3 个月后明显增加,股骨骨密度也明显高于对照组,而服药 3 个月的时间与大鼠骨重建周期为 3 个月是一致的[13]。血清骨钙素和抗酒石酸性磷酸酶 5b 的检测结果表明,口服淫羊藿苷使大鼠体内骨形成水平提高而骨吸收水平降低,是骨密度得以提高的主要原因。

骨质量主要与骨组织微结构有关,而 μCT 可以准确并直观反映反映骨微结构和形态[14]。本实验 μCT 检测发现,淫羊藿苷使骨体积百分率、骨小梁数量和骨小梁厚度增加,同时使骨小梁分离度和模型系数显著下降,表明口服淫羊藿苷能使骨小梁数和骨小梁厚度增加,提高骨小梁的网状结构交联度,从而使大鼠骨质紧密,明显改善骨微结构。骨生物力学参数可较直接地反映骨的抗骨折能力,本实验中,淫羊藿苷组大鼠的股骨最大载荷、弹性模量和屈服强度均显著提高,表明口服淫羊藿苷显著提高了大鼠的生物力学性能,即抗骨折的能力。

综上所述,给幼年大鼠灌服淫羊藿苷 3 个月后,大鼠骨密度显著增加,以骨组织微结构为主要指证的骨质量明显改善,因而其骨的生物性能,即抗骨折的能力显著提高,其作用机理可能是提高骨形成而抑制骨吸收。本实验首次证明口服淫羊藿苷可以提高大鼠骨强度而预防骨质疏松,对于预防骨质疏松和骨质疏松性骨折具有十分重要的意义。

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口服淫羊藿苷可提高大鼠的峰值骨密度和骨质量

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