

· 临床研究 ·

健腰密骨颗粒联合碳酸钙 D3 片口服 治疗骨量减少合并腰痛的临床研究

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摘要 目的:观察健腰密骨颗粒联合碳酸钙 D3 片口服治疗骨量减少合并腰痛的临床疗效,并初步探讨其作用机制。**方法:**将符合要求的 108 例骨量减少合并腰痛患者随机分为 2 组,每组 54 例,分别采用健腰密骨颗粒联合碳酸钙 D3 片口服治疗(健腰密骨颗粒组)和健腰密骨颗粒模拟剂联合碳酸钙 D3 片口服治疗(健腰密骨颗粒模拟剂组)。碳酸钙 D3 片每天口服 1 次,每次 600 mg;健腰密骨颗粒及健腰密骨颗粒模拟剂每天口服 2 次,每次 11 g。分别于治疗前和治疗开始后 6 个月,测定 2 组患者 $L_1 \sim L_4$ 骨密度、股骨颈骨密度及血清碱性磷酸酶(alkaline phosphatase, ALP)、骨 γ -羧基谷氨酸蛋白(bone γ -carboxy-glutamic acid protein, BGP)、I 型前胶原羧基末端前肽(carboxy terminal propeptide of type I procollagen, P I NP)、 β -I 型胶原交联 C-末端肽(β isomer of C-terminal telopeptide of type I collagen, β -CTX)、25-羟基维生素 D 及促甲状腺激素(thyroid-stimulating hormone, TSH)含量;于治疗前和治疗开始后 1、3、6 个月,采用视觉模拟量表(visual analogue scale, VAS)评价腰部疼痛情况,采用 Oswestry 功能障碍指数(Oswestry disability index, ODI)评价腰部功能。**结果:**① $L_1 \sim L_4$ 骨密度。治疗前、治疗开始后 6 个月,2 组患者 $L_1 \sim L_4$ 骨密度 T 值比较,组间差异均无统计学意义(-1.54 ± 0.66 , -1.54 ± 0.75 , $t = -0.050$, $P = 0.822$; -1.40 ± 1.03 , -1.39 ± 0.88 , $t = -0.033$, $P = 0.974$);2 组患者治疗开始后 6 个月 $L_1 \sim L_4$ 骨密度 T 值与治疗前比较,差异均无统计学意义($t = -1.046$, $P = 0.301$; $t = -1.395$, $P = 0.178$)。②股骨颈骨密度。治疗前、治疗开始后 6 个月,2 组患者股骨颈骨密度 T 值比较,组间差异均无统计学意义(-1.46 ± 0.67 , -1.53 ± 0.79 , $t = 0.434$, $P = 0.327$; -1.38 ± 0.84 , -1.49 ± 0.78 , $t = 0.677$, $P = 0.500$);2 组患者治疗开始后 6 个月股骨颈骨密度 T 值与治疗前比较,差异均无统计学意义($t = -1.046$, $P = 0.301$; $t = -1.395$, $P = 0.178$)。③腰部疼痛 VAS 评分。时间因素和分组因素不存在交互效应($F = 0.054$, $P = 0.984$);2 组患者的腰部疼痛 VAS 评分总体比较,组间差异无统计学意义,即不存在分组效应($F = 0.099$, $P = 0.754$);治疗前后不同时间点腰部疼痛 VAS 评分的差异有统计学意义,即存在时间效应($F = 31.840$, $P = 0.000$);2 组患者腰部疼痛 VAS 评分随时间变化均呈下降趋势,但 2 组的下降趋势不完全一致[(4.85 ± 1.41)分, (3.21 ± 1.55)分, (2.10 ± 0.89)分, (1.24 ± 0.86)分, $F = 17.646$, $P = 0.001$; (4.75 ± 1.75)分, (3.81 ± 1.77)分, (3.32 ± 1.97)分, (2.35 ± 2.27)分, $F = 14.210$, $P = 0.001$];治疗前、治疗开始后 1 个月,2 组患者腰部疼痛 VAS 评分比较,组间差异均无统计学意义($t = 0.327$, $P = 0.744$; $t = -1.493$, $P = 0.136$);治疗开始后 3 个月、6 个月,健腰密骨颗粒组患者腰部疼痛 VAS 评分均低于健腰密骨颗粒模拟剂组($t = -3.233$, $P = 0.001$; $t = -4.204$, $P = 0.001$)。④ODI。时间因素和分组因素不存在交互效应($F = 0.058$, $P = 0.982$);2 组患者的 ODI 总体比较,组间差异无统计学意义,即不存在分组效应($F = 0.312$, $P = 0.577$);治疗前后不同时间点 ODI 的差异有统计学意义,即存在时间效应($F = 59.057$, $P = 0.000$);2 组患者 ODI 随时间变化均呈下降趋势,但 2 组的下降趋势不完全一致[(35.14 ± 2.27)%, (29.92 ± 1.60)%, (22.71 ± 1.52)%, (15.19 ± 0.86)%, $F = 28.063$, $P = 0.000$; (34.98 ± 1.91)%, (30.70 ± 1.57)%, (23.74 ± 1.46)%, (16.01 ± 0.75)%, $F = 31.384$, $P = 0.000$];治疗前、治疗开始后 1 个月,2 组患者 ODI 比较,组间差异均无统计学意义($t = -0.055$, $P = 0.956$; $t = -1.349$, $P = 0.278$);治疗开始后 3 个月、6 个月,健腰密骨颗粒组患者 ODI 均低于健腰密骨颗粒模拟剂组($t = -3.627$, $P = 0.003$; $t = -4.471$, $P = 0.001$)。⑤血清 ALP 含量。治疗前、治疗开始后 6 个月,2 组患者血清 ALP 含量比较,组间差异均无统计学意义[(72.96 ± 16.51)IU \cdot L $^{-1}$, (75.91 ± 28.94)IU \cdot L $^{-1}$, $t = -0.649$, $P = 0.518$; (82.06 ± 39.26)IU \cdot L $^{-1}$, (79.43 ± 19.34)IU \cdot L $^{-1}$, $t = 0.422$, $P = 0.674$];2 组患者治疗开始后 6 个月血清 ALP 含量与治疗前比较,差异均无统计学意义($t = -1.785$, $P = 0.080$; $t = -0.794$, $P = 0.431$)。⑥血清 BGP 含量。治疗前、治疗开始后 6 个月,2 组患者血清 BGP 含量比较,组间差异均无统计学意义[(14.44 ± 5.57)ng \cdot mL $^{-1}$, (14.23 ± 4.80)ng \cdot mL $^{-1}$, $t = 0.214$, $P = 0.831$; (13.64 ± 4.65)ng \cdot mL $^{-1}$, (14.25 ± 4.28)ng \cdot mL $^{-1}$, $t = -0.676$, $P = 0.501$];2 组患者治疗开始后 6 个月血清 BGP 含量与治疗前比较,差异均无统计学意义($t = 0.347$, $P = 0.730$; $t = -0.234$, $P = 0.816$)。⑦血清 P I NP 含量。治疗前、治疗

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开始后 6 个月, 2 组患者血清 P I NP 含量比较, 组间差异均无统计学意义[$(44.93 \pm 24.00) \text{ ng} \cdot \text{mL}^{-1}$, $(40.56 \pm 17.30) \text{ ng} \cdot \text{mL}^{-1}$, $t = 1.087$, $P = 0.280$; $(44.95 \pm 18.53) \text{ ng} \cdot \text{mL}^{-1}$, $(44.21 \pm 15.44) \text{ ng} \cdot \text{mL}^{-1}$, $t = 0.217$, $P = 0.828$]; 2 组患者治疗开始后 6 个月血清 P I NP 含量和治疗前比较, 差异均无统计学意义($t = -0.442$, $P = 0.661$; $t = -1.569$, $P = 0.123$)。⑧血清 β -CTX 含量。治疗前、治疗开始后 6 个月, 2 组患者血清 β -CTX 含量比较, 组间差异均无统计学意义[$(0.36 \pm 0.21) \text{ ng} \cdot \text{mL}^{-1}$, $(0.33 \pm 0.16) \text{ ng} \cdot \text{mL}^{-1}$, $t = 0.743$, $P = 0.759$; $(0.38 \pm 0.18) \text{ ng} \cdot \text{mL}^{-1}$, $(0.36 \pm 0.15) \text{ ng} \cdot \text{mL}^{-1}$, $t = 0.604$, $P = 0.548$]; 2 组患者治疗开始后 6 个月血清 β -CTX 含量和治疗前比较, 差异均无统计学意义($t = -1.325$, $P = 0.191$; $t = -1.024$, $P = 0.311$)。⑨血清 25-羟基维生素 D 含量。治疗前、治疗开始后 6 个月, 2 组患者血清 25-羟基维生素 D 含量比较, 组间差异均无统计学意义[$(20.24 \pm 8.01) \text{ ng} \cdot \text{mL}^{-1}$, $(19.53 \pm 7.12) \text{ ng} \cdot \text{mL}^{-1}$, $t = 0.490$, $P = 0.625$; $(21.80 \pm 6.87) \text{ ng} \cdot \text{mL}^{-1}$, $(23.71 \pm 5.82) \text{ ng} \cdot \text{mL}^{-1}$, $t = -1.490$, $P = 0.139$]; 健腰密骨颗粒组患者治疗开始后 6 个月血清 25-羟基维生素 D 含量和治疗前比较, 差异无统计学意义($t = -1.811$, $P = 0.076$); 健腰密骨颗粒模拟剂组患者治疗开始后 6 个月血清 25-羟基维生素 D 含量高于治疗前($t = -3.648$, $P = 0.001$)。⑩血清 TSH 含量。治疗前, 2 组患者血清 TSH 含量比较, 差异无统计学意义[$(2.89 \pm 1.52) \mu\text{IU} \cdot \text{mL}^{-1}$, $(2.59 \pm 1.56) \mu\text{IU} \cdot \text{mL}^{-1}$, $t = 1.031$, $P = 0.305$]; 治疗开始后 6 个月, 健腰密骨颗粒组患者血清 TSH 含量高于健腰密骨颗粒模拟剂组[$(3.33 \pm 1.99) \mu\text{IU} \cdot \text{mL}^{-1}$, $(2.51 \pm 1.30) \mu\text{IU} \cdot \text{mL}^{-1}$, $t = 2.41$, $P = 0.018$]; 健腰密骨颗粒组患者治疗开始后 6 个月血清 TSH 含量高于治疗前($t = -2.106$, $P = 0.040$); 健腰密骨颗粒模拟剂组患者治疗开始后 6 个月血清 TSH 含量和治疗前比较, 差异无统计学意义($t = -0.412$, $P = 0.682$)。结论: 现有的证据表明, 采用健腰密骨颗粒联合碳酸钙 D3 片口服, 能够缓解骨量减少合并腰痛患者的腰痛症状、改善腰部功能、提高血清 TSH 含量, 但其改善骨密度和血清骨代谢指标的作用不明确, 尚需进一步扩大样本量、延长随访观察时间。

关键词 骨疾病; 代谢性; 骨量减少; 骨密度; 腰痛; 健腰密骨颗粒; 模拟剂; 碳酸钙; 维生素 D3; 双盲法; 随机对照试验专题

A clinical study of oral applications of Jianyao Migu(健腰密骨) granules and calcium carbonate and Vitamin D3 tablets for treatment of osteopenia combined with low back pain

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ABSTRACT **Objective:** To observe the clinical outcomes of oral applications of Jianyao Migu(健腰密骨, JYMG) granules and calcium carbonate and Vitamin D3 tablets for treatment of osteopenia combined with low back pain, and to explore its mechanism of action. **Methods:** One hundred and eight patients with osteopenia and low back pain were enrolled in the study and were randomly divided into JYMG granule group and JYMG granule mimetic agent group by using random digits table, 54 cases in each group. The patients in JYMG granule group were treated with oral applications of JYMG granules(twice a day, 11 g at a time) and calcium carbonate and Vitamin D3 tablets(once a day, 600 mg at a time) for consecutive 6 months; while the others in JYMG granule mimetic agent group with oral applications of JYMG granule mimetic agent(twice a day, 11 g at a time) and calcium carbonate and Vitamin D3 tablets(once a day, 600 mg at a time) for consecutive 6 months. The bone mineral densities(BMDs) of lumbar vertebrae(LV) from L₁ to L₄ and femur neck as well as the serum levels of alkaline phosphatase(ALP), bone γ -carboxy-glutamic acid protein(BGP), carboxy terminal propeptide of type I procollagen(P I NP), β isomer of C-terminal telopeptide of type I collagen(β -CTX), 25-hydroxy vitamin D(25(OH)D) and thyroid-stimulating hormone(TSH) were detected before the treatment and at 6 months after the beginning of the treatment respectively. Moreover, the low back pain and lumbar function were evaluated by using visual analogue scale(VAS) and Oswestry disability index(ODI) respectively before the treatment and at 1, 3 and 6 months after the beginning of the treatment. **Results:** ①There was no statistical difference in the T value of BMD of LV from L₁ to L₄ between the 2 groups before the treatment and at 6 months after the beginning of the treatment(-1.54 ± 0.66 vs -1.54 ± 0.75 , $t = -0.050$, $P = 0.822$; -1.40 ± 1.03 vs -1.39 ± 0.88 , $t = -0.033$, $P = 0.974$), and there was no statistical difference between the 2 timepoints in the 2 groups($t = -1.046$, $P = 0.301$; $t = -1.395$, $P = 0.178$). ②There was no statistical difference in the T value of BMD of femur neck between the 2 groups before the treatment and at 6 months after the beginning of the treatment(-1.46 ± 0.67 vs -1.53 ± 0.79 , $t = 0.434$, $P = 0.327$; -1.38 ± 0.84 vs -1.49 ± 0.78 , $t = 0.677$, $P = 0.500$), and there was no statistical difference between the 2 timepoints in the 2 groups($t = -1.046$, $P = 0.301$; $t = -1.395$, $P = 0.178$). ③There was no interaction between time factor and group factor in low back pain VAS scores($F = 0.054$, $P = 0.984$). There was no statistical difference in the low back pain VAS scores

between the 2 groups in general, in other words, there was no group effect ($F = 0.099, P = 0.754$). There was statistical difference in the low back pain VAS scores between different timepoints before and after the treatment, in other words, there was time effect ($F = 31.840, P = 0.000$). The low back pain VAS scores presented a downward trend over time in the 2 groups, while the 2 groups were inconsistent with each other in the variation tendency ($4.85 \pm 1.41, 3.21 \pm 1.55, 2.10 \pm 0.89, 1.24 \pm 0.86$ points, $F = 17.646, P = 0.001$; $4.75 \pm 1.75, 3.81 \pm 1.77, 3.32 \pm 1.97, 2.35 \pm 2.27$ points, $F = 14.210, P = 0.001$). There was no statistical difference in low back pain VAS scores between the 2 groups before the treatment and at 1 month after the beginning of the treatment ($t = 0.327, P = 0.744$; $t = -1.493, P = 0.136$), while the low back pain VAS scores decreased in JYMG granule group compared to JYMG granule mimetic agent group at 3 and 6 months after the beginning of the treatment ($t = -3.233, P = 0.001$; $t = -4.204, P = 0.001$). ④ There was no interaction between time factor and group factor in ODI ($F = 0.058, P = 0.982$). There was no statistical difference in ODI between the 2 groups in general, in other words, there was no group effect ($F = 0.312, P = 0.577$). There was statistical difference in ODI between different timepoints before and after the treatment, in other words, there was time effect ($F = 59.057, P = 0.000$). The ODI presented a downward trend over time in the 2 groups, while the 2 groups were inconsistent with each other in the variation tendency ($35.14 \pm 2.27, 29.92 \pm 1.60, 22.71 \pm 1.52, 15.19 \pm 0.86\%$, $F = 28.063, P = 0.000$; $34.98 \pm 1.91, 30.70 \pm 1.57, 23.74 \pm 1.46, 16.01 \pm 0.75\%$, $F = 31.384, P = 0.000$). There was no statistical difference in ODI between the 2 groups before the treatment and at 1 month after the beginning of the treatment ($t = -0.055, P = 0.956$; $t = -1.349, P = 0.278$), while the ODI decreased in JYMG granule group compared to JYMG granule mimetic agent group at 3 and 6 months after the beginning of the treatment ($t = -3.627, P = 0.003$; $t = -4.471, P = 0.001$). ⑤ There was no statistical difference in the serum level of ALP between the 2 groups before the treatment and at 6 months after the beginning of the treatment (72.96 ± 16.51 vs 75.91 ± 28.94 IU/L, $t = -0.649, P = 0.518$; 82.06 ± 39.26 vs 79.43 ± 19.34 IU/L, $t = 0.422, P = 0.674$), and there was no statistical difference between the 2 timepoints in the 2 groups ($t = -1.785, P = 0.080$; $t = -0.794, P = 0.431$). ⑥ There was no statistical difference in the serum level of BGP between the 2 groups before the treatment and at 6 months after the beginning of the treatment (14.44 ± 5.57 vs 14.23 ± 4.80 ng/mL, $t = 0.214, P = 0.831$; 13.64 ± 4.65 vs 14.25 ± 4.28 ng/mL, $t = -0.676, P = 0.501$), and there was no statistical difference between the 2 timepoints in the 2 groups ($t = 0.347, P = 0.730$; $t = -0.234, P = 0.816$). ⑦ There was no statistical difference in the serum level of P I NP between the 2 groups before the treatment and at 6 months after the beginning of the treatment (44.93 ± 24.00 vs 40.56 ± 17.30 ng/mL, $t = 1.087, P = 0.280$; 44.95 ± 18.53 vs 44.21 ± 15.44 ng/mL, $t = 0.217, P = 0.828$), and there was no statistical difference between the 2 timepoints in the 2 groups ($t = -0.442, P = 0.661$; $t = -1.569, P = 0.123$). ⑧ There was no statistical difference in the serum level of β -CTX between the 2 groups before the treatment and at 6 months after the beginning of the treatment (0.36 ± 0.21 vs 0.33 ± 0.16 ng/mL, $t = 0.743, P = 0.759$; 0.38 ± 0.18 vs 0.36 ± 0.15 ng/mL, $t = 0.604, P = 0.548$), and there was no statistical difference between the 2 timepoints in the 2 groups ($t = -1.325, P = 0.191$; $t = -1.024, P = 0.311$). ⑨ There was no statistical difference in the serum level of 25(OH)D between the 2 groups before the treatment and at 6 months after the beginning of the treatment (20.24 ± 8.01 vs 19.53 ± 7.12 ng/mL, $t = 0.490, P = 0.625$; 21.80 ± 6.87 vs 23.71 ± 5.82 ng/mL, $t = -1.490, P = 0.139$). There was no statistical difference in the serum level of 25(OH)D between the 2 timepoints in JYMG granule group ($t = -1.811, P = 0.076$), while the serum level of 25(OH)D was higher at 6 months after the beginning of the treatment compared to pre-treatment in JYMG granule mimetic agent group ($t = -3.648, P = 0.001$). ⑩ There was no statistical difference in the serum level of TSH between the 2 groups before the treatment (2.89 ± 1.52 vs 2.59 ± 1.56 μ IU/mL, $t = 1.031, P = 0.305$). The serum level of TSH was higher in JYMG granule group compared to JYMG granule mimetic agent group at 6 months after the beginning of the treatment (3.33 ± 1.99 vs 2.51 ± 1.30 μ IU/mL, $t = 2.41, P = 0.018$). The serum level of TSH was higher at 6 months after the beginning of the treatment compared to pre-treatment in JYMG granule group ($t = -2.106, P = 0.040$), while there was no statistical difference in the serum level of TSH between the 2 timepoints in JYMG granule mimetic agent group ($t = -0.412, P = 0.682$). **Conclusion:** Available evidences suggest that oral applications of JYMG granules and calcium carbonate and Vitamin D3 tablets can relieve low back pain, improve low back function and increase the serum level of TSH in patients with osteopenia and low back pain. However, its effect of improving BMD and serum bone metabolism indexes is unclear, so the larger sample size and longer follow-up time are needed for the further study.

Keywords bone diseases; metabolic; osteopenia; bone density; low back pain; Jianyao Migu Granules; placebos; calcium carbonate; vitamin D3; double-blind method; randomized controlled trials as topic

骨量减少是骨质疏松症的前一阶段。中国骨质疏松症流行病学调查结果显示,我国 40~49 岁人群中

骨量减少者的占比为 32.9%, 50 岁以上人群中骨量减少者的占比为 46.4%^[1]。部分骨量减少患者伴有疼痛症状, 且以腰背部疼痛为主。在骨量减少阶段及时进行干预, 能够有效延缓或遏制骨质疏松症的进展。健腰密骨颗粒是国医大师施杞教授基于“以气为主, 以血为先”的理论, 结合其临床经验而总结出来的治疗骨质疏松症的经验方。前期动物实验研究^[2-3]结果表明, 健腰密骨片(与健腰密骨颗粒同方)能够提高小鼠椎体骨密度。为了进一步观察健腰密骨颗粒治疗骨量减少合并腰痛的临床疗效和安全性, 并初步探讨其可能的作用机制, 我们开展了一项多中心、随机、双盲、对照临床试验, 现总结报告如下。

1 临床资料

1.1 一般资料 选取 2016 年 12 月至 2018 年 12 月在上海市静安区彭浦新村社区卫生服务中心、上海市浦东新区上钢社区卫生服务中心、上海市浦东新区南码头社区卫生服务中心就诊的骨量减少合并腰痛患者为研究对象。试验方案经医院医学伦理委员会审查通过。

1.2 纳入标准 ① $-2.5 < \text{骨密度 T 值} < -1$ ^[4]; ②女性年龄 50~75 岁, 男性年龄 60~75 岁; ③腰背疼痛视觉模拟量表(visual analogue scale, VAS) 评分 ≥ 4 分; ④近 3 个月内未接受相关治疗; ⑤同意参与本研究, 签署知情同意书。

1.3 排除标准 ①过敏体质者; ②合并内分泌疾病者; ③合并类风湿关节炎及其他免疫性疾病者; ④合并肿瘤、结核、炎症等导致的腰痛者; ⑤合并骨折者; ⑥有精神病史或智力障碍者。

2 方法

2.1 分组方法 采用随机数字表将符合要求的患者随机分为健腰密骨颗粒组和健腰密骨颗粒模拟剂组, 分组情况对患者和研究者均隐藏。

2.2 治疗方法 2 组患者均口服碳酸钙 D3 片(钙尔奇 D 片, 惠氏制药有限公司生产, 批准文号: 国药准字 H10950029), 每天 1 次, 每次 600 mg(1 片), 连续服

用 6 个月。健腰密骨颗粒组患者服用健腰密骨颗粒, 健腰密骨颗粒模拟剂组服用健腰密骨颗粒模拟剂, 均每天 2 次, 每次 11 g(1 袋), 连续服用 6 个月。健腰密骨颗粒、健腰密骨颗粒模拟剂均由四川新绿色药业有限公司制备。健腰密骨颗粒药物组成包括黄芪 15 g、淫羊藿 12 g、墨旱莲 12 g、丹参 9 g、青风藤 9 g、牛膝 9 g。健腰密骨颗粒模拟剂组成成分为 2% 的焦糖色素、0.35% 的柠檬黄色素、0.04% 的日落黄色素、0.04% 的蔗糖八乙酸酯及麦芽糊精。

2.3 疗效和安全性评价方法 分别于治疗前和治疗开始后 6 个月, 测定 2 组患者 $L_1 \sim L_4$ 骨密度、股骨颈骨密度及血清碱性磷酸酶(alkaline phosphatase, ALP)、骨 γ -羧基谷氨酸蛋白(bone γ -carboxy-glutamic acid protein, BGP)、I 型前胶原羧基末端前肽(carboxy terminal propeptide of type I procollagen, P I NP)、 β -I 型胶原交联 C-末端肽(β isomer of C-terminal telopeptide of type I collagen, β -CTX)、25-羟基维生素 D 及促甲状腺激素(thyroid-stimulating hormone, TSH) 含量; 于治疗前和治疗开始后 1、3、6 个月, 采用视觉模拟量表(visual analogue scale, VAS) 评价腰部疼痛情况, 采用 Oswestry 功能障碍指数(Oswestry disability index, ODI) 评价腰部功能^[5]。

2.4 数据统计方法 采用 SPSS21.0 统计软件对数据进行统计分析。采用全分析集进行意向性分析, 失访患者的腰部疼痛 VAS 评分和 ODI 缺失数据采用末次观测值结转法进行补充。2 组患者性别的组间比较采用 χ^2 检验, 年龄、体质量指数的组间比较均采用 t 检验, $L_1 \sim L_4$ 骨密度、股骨颈骨密度及血清 ALP、BGP、PINP、 β -CTX、25-羟基维生素 D、TSH 含量的组间、组内比较均采用 t 检验, 腰部疼痛 VAS 评分和 ODI 的比较均采用重复测量资料的方差分析。检验水准 $\alpha = 0.05$ 。

3 结果

3.1 分组结果 共纳入 108 例患者, 健腰密骨颗粒组和对照治疗组各 54 例。2 组患者基线资料比较, 差异无统计学意义, 有可比性(表 1)。

表 1 2 组骨量减少合并腰痛患者基线资料

组别	样本量/例	性别/例		年龄/ ($\bar{x} \pm s$, 岁)	体质量指数/ ($\bar{x} \pm s$, $\text{kg} \cdot \text{m}^{-2}$)
		男	女		
健腰密骨颗粒组	54	5	49	65.65 \pm 6.74	25.10 \pm 3.20
健腰密骨颗粒模拟剂组	54	6	48	66.61 \pm 5.01	23.58 \pm 2.70
检验统计量		$\chi^2 = 0.101$		$t = -0.843$	$t = 1.672$
P 值		0.750		0.401	0.073

3.2 随访结果 健腰密骨颗粒组治疗开始后 3 个月随访时脱落 1 例,治疗开始后 6 个月随访时脱落 3 例;健腰密骨颗粒模拟剂组治疗开始后 6 个月随访时脱落 6 例。

3.3 疗效评价结果

3.3.1 $L_1 \sim L_4$ 骨密度 治疗前、治疗开始后 6 个月,2 组患者 $L_1 \sim L_4$ 骨密度 T 值比较,组间差异均无统计学意义;2 组患者治疗开始后 6 个月 $L_1 \sim L_4$ 骨密度 T 值与治疗前比较,差异均无统计学意义(表 2)。

3.3.2 股骨颈骨密度 治疗前、治疗开始后 6 个月,2 组患者股骨颈骨密度 T 值比较,组间差异均无统计学意义;2 组患者治疗开始后 6 个月股骨颈骨密度 T 值与治疗前比较,差异均无统计学意义(表 3)。

3.3.3 腰部疼痛 VAS 评分 时间因素和分组因素不存在交互效应;2 组患者的腰部疼痛 VAS 评分总体比较,组间差异无统计学意义,即不存在分组效应;治疗前后不同时间点腰部疼痛 VAS 评分的差异有统计学意义,即存在时间效应;2 组患者腰部疼痛 VAS 评分随时间变化均呈下降趋势,但 2 组的下降趋势不完全一致;治疗前、治疗开始后 1 个月,2 组患者腰部疼

痛 VAS 评分比较,差异均无统计学意义;治疗开始后 3 个月、6 个月,健腰密骨颗粒组患者腰部疼痛 VAS 评分均低于健腰密骨颗粒模拟剂组(表 4)。

3.3.4 ODI 时间因素和分组因素不存在交互效应;2 组患者的 ODI 总体比较,组间差异无统计学意义,即不存在分组效应;治疗前后不同时间点 ODI 的差异有统计学意义,即存在时间效应;2 组患者 ODI 随时间变化均呈下降趋势,但 2 组的下降趋势不完全一致;治疗前、治疗开始后 1 个月,2 组患者 ODI 比较,差异无统计学意义;治疗开始后 3 个月、6 个月,健腰密骨颗粒组患者 ODI 均低于健腰密骨颗粒模拟剂组(表 5)。

3.4 血清学指标检测结果

3.4.1 血清 ALP 含量 治疗前、治疗开始后 6 个月,2 组患者血清 ALP 含量比较,组间差异均无统计学意义;2 组患者治疗开始后 6 个月血清 ALP 含量与治疗前比较,差异均无统计学意义(表 6)。

3.4.2 血清 BGP 含量 治疗前、治疗开始后 6 个月,2 组患者血清 BGP 含量比较,组间差异均无统计学意义;2 组患者治疗开始后 6 个月血清 BGP 含量与治疗前比较,差异均无统计学意义(表 7)。

表 2 2 组骨量减少合并腰痛患者治疗前后 $L_1 \sim L_4$ 骨密度 T 值

组别	样本量/例	$L_1 \sim L_4$ 骨密度 T 值($\bar{x} \pm s$)		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	-1.54 ± 0.66	-1.40 ± 1.03	-1.046	0.301
健腰密骨颗粒模拟剂组	48	-1.54 ± 0.75	-1.39 ± 0.88	-1.395	0.178
t 值		-0.050	-0.033		
P 值		0.822	0.974		

表 3 2 组骨量减少合并腰痛患者治疗前后股骨颈骨密度 T 值

组别	样本量/例	股骨颈骨密度 T 值($\bar{x} \pm s$)		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	-1.46 ± 0.67	-1.38 ± 0.84	-1.046	0.301
健腰密骨颗粒模拟剂组	48	-1.53 ± 0.79	-1.49 ± 0.78	-1.395	0.178
t 值		0.434	0.677		
P 值		0.327	0.500		

表 4 2 组骨量减少合并腰痛患者治疗前后腰部疼痛视觉模拟量表评分

组别	样本量/例	腰部疼痛视觉模拟量表评分/($\bar{x} \pm s$, 分)					F 值	P 值
		治疗前	治疗开始后 1 个月	治疗开始后 3 个月	治疗开始后 6 个月	合计		
健腰密骨颗粒组	54	4.85 ± 1.41	3.21 ± 1.55	2.10 ± 0.89	1.24 ± 0.86	3.56 ± 0.14	17.646	0.001
健腰密骨颗粒模拟剂组	54	4.75 ± 1.75	3.81 ± 1.77	3.32 ± 1.97	2.35 ± 2.27	3.62 ± 0.14	14.210	0.001
合计	108	4.80 ± 0.15	3.86 ± 0.15	3.29 ± 0.19	2.40 ± 0.21	3.59 ± 0.10	31.840 ¹⁾	0.000 ¹⁾
检验统计量		t = 0.327	t = -1.493	t = -3.233	t = -4.204	0.099 ¹⁾	F = 0.054 ²⁾ , P = 0.984 ²⁾	
P 值		0.744	0.136	0.001	0.001	0.754 ¹⁾		

1) 主效应的 F 值和 P 值; 2) 交互效应的 F 值和 P 值。

3.4.3 血清 P I NP 含量 治疗前、治疗开始后 6 个月, 2 组患者血清 P I NP 含量比较, 组间差异均无统计学意义; 2 组患者治疗开始后 6 个月血清 P I NP 含量和治疗前比较, 差异均无统计学意义 (表 8)。

3.4.4 血清 β - CTX 含量 治疗前、治疗开始后 6 个月, 2 组患者血清 β - CTX 含量比较, 组间差异均无统计学意义; 2 组患者治疗开始后 6 个月血清 β - CTX 含量和治疗前比较, 差异均无统计学意义 (表 9)。

3.4.5 血清 25 - 羟基维生素 D 含量 治疗前、治疗开始后 6 个月, 2 组患者血清 25 - 羟基维生素 D 含量

组间比较, 差异均无统计学意义; 健腰密骨颗粒组患者治疗开始后 6 个月血清 25 - 羟基维生素 D 含量和治疗前比较, 差异无统计学意义; 健腰密骨颗粒模拟剂组患者治疗开始后 6 个月血清 25 - 羟基维生素 D 含量高于治疗前 (表 10)。

3.4.6 血清 TSH 含量 治疗前, 2 组患者血清 TSH 含量比较, 差异无统计学意义; 治疗开始后 6 个月, 健腰密骨颗粒组血清 TSH 含量高于健腰密骨颗粒模拟剂组; 健腰密骨颗粒组患者治疗开始后 6 个月血清 TSH 含量高于治疗前; 健腰密骨颗粒模拟剂组患者治疗开始后 6 个月血清 TSH 含量和治疗前比较, 差异无统计学意义 (表 11)。

表 5 2 组骨量减少合并腰痛患者治疗前后 Oswestry 功能障碍指数

组别	样本量/ 例	Oswestry 功能障碍指数/ $(\bar{x} \pm s, \%)$					F 值	P 值
		治疗前	治疗开始后 1 个月	治疗开始后 3 个月	治疗开始后 6 个月	合计		
健腰密骨颗粒组	54	35.14 \pm 2.27	29.92 \pm 1.60	22.71 \pm 1.52	15.19 \pm 0.86	25.74 \pm 0.96	28.063	0.000
健腰密骨颗粒模拟剂组	54	34.98 \pm 1.91	30.70 \pm 1.57	23.74 \pm 1.46	16.01 \pm 0.75	26.35 \pm 0.88	31.384	0.000
合计	108	35.06 \pm 1.48	30.31 \pm 1.11	23.23 \pm 1.05	15.60 \pm 0.57	26.05 \pm 0.65	59.057 ¹⁾	0.000 ¹⁾
检验统计量		$t = -0.055$	$t = -1.349$	$t = -3.627$	$t = -4.471$	0.312 ¹⁾	$F = 0.058^{2)}$, $P = 0.982^{2)}$	
P 值		0.956	0.278	0.003	0.001	0.577 ¹⁾		

1) 主效应的 F 值和 P 值; 2) 交互效应的 F 值和 P 值。

表 6 2 组骨量减少合并腰痛患者治疗前后血清碱性磷酸酶含量

组别	样本量/例	血清碱性磷酸酶含量/ $(\bar{x} \pm s, \text{IU} \cdot \text{L}^{-1})$		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	72.96 \pm 16.51	82.06 \pm 39.26	-1.785	0.080
健腰密骨颗粒模拟剂组	48	75.91 \pm 28.94	79.43 \pm 19.34	-0.794	0.431
t 值		-0.649	0.422		
P 值		0.518	0.674		

表 7 2 组骨量减少合并腰痛患者治疗前后骨 γ - 羧基谷氨酸蛋白含量

组别	样本量/例	骨 γ - 羧基谷氨酸蛋白含量/ $(\bar{x} \pm s, \text{ng} \cdot \text{mL}^{-1})$		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	14.44 \pm 5.57	13.64 \pm 4.65	0.347	0.730
健腰密骨颗粒模拟剂组	48	14.23 \pm 4.80	14.25 \pm 4.28	-0.234	0.816
t 值		0.214	-0.676		
P 值		0.831	0.501		

表 8 2 组骨量减少合并腰痛患者治疗前后血清 I 型前胶原羧基末端前肽含量

组别	样本量/例	血清 I 型前胶原羧基末端前肽含量/ $(\bar{x} \pm s, \text{ng} \cdot \text{mL}^{-1})$		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	44.93 \pm 24.00	44.95 \pm 18.53	-0.442	0.661
健腰密骨颗粒模拟剂组	48	40.56 \pm 17.30	44.21 \pm 15.44	-1.569	0.123
t 值		1.087	0.217		
P 值		0.280	0.828		

表 9 2 组骨量减少合并腰痛患者治疗前后血清 β -I 型胶原交联 C-末端肽含量

组别	样本量/例	血清 β -I 型胶原交联 C-末端肽含量/ ($\bar{x} \pm s, \text{ng} \cdot \text{mL}^{-1}$)		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	0.36 ± 0.21	0.38 ± 0.18	-1.325	0.191
健腰密骨颗粒模拟剂组	48	0.33 ± 0.16	0.36 ± 0.15	-1.024	0.311
t 值		0.743	0.604		
P 值		0.759	0.548		

表 10 2 组骨量减少合并腰痛患者治疗前后血清 25-羟基维生素 D 含量

组别	样本量/例	血清 25-羟基维生素 D 含量/ ($\bar{x} \pm s, \text{ng} \cdot \text{mL}^{-1}$)		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	20.24 ± 8.01	21.80 ± 6.87	-1.811	0.076
健腰密骨颗粒模拟剂组	48	19.53 ± 7.12	23.71 ± 5.82	-3.648	0.001
t 值		0.490	-1.490		
P 值		0.625	0.139		

表 11 2 组骨量减少合并腰痛患者治疗前后血清促甲状腺激素含量

组别	样本量/例	血清促甲状腺激素含量/ ($\bar{x} \pm s, \mu\text{IU} \cdot \text{mL}^{-1}$)		t 值	P 值
		治疗前	治疗开始后 6 个月		
健腰密骨颗粒组	50	2.89 ± 1.52	3.33 ± 1.99	-2.106	0.040
健腰密骨颗粒模拟剂组	48	2.59 ± 1.56	2.51 ± 1.30	-0.412	0.682
t 值		1.031	2.410		
P 值		0.305	0.018		

4 讨 论

骨质疏松症属中医学“骨痹”“骨痿”的范畴。《素问·痿论》曰：“肾主身之骨髓……肾气热，则腰脊不举，骨枯而髓减，发为骨痿。”相关研究^[6]亦表明肾为骨质疏松的主要病位。健腰密骨颗粒以黄芪、淫羊藿为君，益气补肾、强筋壮骨；以墨旱莲为臣药，与淫羊藿配伍以达阴阳双补之效；以青风藤、丹参为佐药，可化瘀通络止痛；牛膝为使药，引诸药下行。本研究结果显示，在治疗开始后 3 个月、6 个月，健腰密骨颗粒组患者的腰部疼痛 VAS 评分、ODI 均低于健腰密骨颗粒组；提示健腰密骨颗粒在缓解骨量减少合并的腰部疼痛及改善腰部功能方面具有显著优势。目前，健腰密骨颗粒缓解腰部疼痛的现代药理尚不明确。研究表明，骨质疏松合并的区域疼痛主要有神经病理性疼痛和区域炎症性疼痛^[7]。淫羊藿的主要有效成分是淫羊藿苷，其具有类雌激素样作用，能够促进骨细胞增殖和分化^[8-9]；牛膝中的牛膝总皂苷具有抑制破骨细胞活性，促进骨形成的作用^[10]；青藤碱既可以直接缓解慢性疼痛，又可以通过缓解炎症、促进神经功能重塑来缓解慢性疼痛^[11]。前期动物实验研

究^[2-3]结果表明，健腰密骨片（与健腰密骨颗粒同方）能够通过激活骨形态发生蛋白、BGP、骨髓间充质干细胞的表达，促进成骨细胞增殖与分化，提高小鼠椎体骨密度；前期多中心临床试验^[12]结果显示，骨量减少患者服用健腰密骨颗粒 12 个月后，髌部骨密度高于治疗前。本研究结果显示，健腰密骨颗粒组患者服用健腰密骨颗粒 6 个月后， $L_1 \sim L_4$ 骨密度和股骨颈骨密度与治疗前比较，差异无统计学意义，且健腰密骨颗粒组与健腰密骨颗粒模拟剂组比较亦无显著差异；分析其可能与患者服用时间较短，而骨密度变化周期较长有关。

血清 TSH 含量与骨密度关系密切。Kim 等^[13-19]研究发现，血清 TSH 含量与骨密度呈正相关，低血清 TSH 含量是老年骨质疏松性椎体骨折发生的独立危险因素。Abe 等^[20]研究发现，TSH 受体在成骨细胞和破骨细胞上均有表达，TSH 作用于成骨细胞和破骨细胞生成的前期，能够通过多种途径发挥调解骨代谢的作用。此外，Sampath 等^[21]研究发现，给予切除卵巢的大鼠注射低剂量的 TSH，其能够通过抑制骨吸收和促进骨形成影响骨重塑。本研究发现，口服健腰密

骨颗粒能够提高患者的血清 TSH 含量,但对于血清 ALP、BGP、P I NP、 β -CTX、25-羟基维生素 D 含量均无显著影响,这可能与中药复方制剂作用靶点复杂、本研究观察时间较短有关。因此,健腰密骨颗粒治疗骨量减少合并腰部疼痛的作用机制及 TSH 在其中的作用尚需进一步研究。

现有的证据表明,采用健腰密骨颗粒联合碳酸钙 D3 片口服,能够缓解骨量减少合并腰痛患者的腰痛症状、改善腰部功能、提高血清 TSH 含量,但其改善骨密度和血清骨代谢指标的作用不明确,尚需进一步扩大样本量、延长随访观察时间。

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