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·药物研究·

辛伐他汀对绝经伴血脂代谢异常女性跟骨骨密度的影响

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摘要:**目的** 研究辛伐他汀对绝经后伴血脂代谢异常女性跟骨骨密度的影响。**方法** 分析 885 名绝经后口服辛伐他汀治疗血脂代谢异常(TC>5.18 mmol/L 或 LDL-C> 3.37 mmol/L)女性的跟骨骨密度,并依据 *T* 值分为骨质正常、骨量减少、骨质疏松。**结果** 治疗前跟骨骨密度为 305.3± 59.2 mg/cm^2,骨质正常、骨量减少、骨质疏松的人数分别为 115、446、324,口服辛伐他汀(20 mg/d)治疗 3 月后骨密度为 309.7±56.3 mg/cm^2,骨质正常、骨量减少、骨质疏松的人数为 117、459、319,12 月后跟骨骨密度为 312.5±60.9 mg/cm^2,骨质正常、骨量减少、骨质疏松的人数为 122、460、303。**结论** 绝经后伴血脂代谢异常女性应用辛伐他汀(20 mg/d)治疗 12 个月后跟骨骨密度增高,但对骨质疏松患病风险无影响。

关键词:辛伐他汀;绝经;血脂代谢异常;骨密度

Effect of simvastatin on bone mineral density of the calcaneus in postmenopausal women with hyperlipoidemia

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Abstract: **Objective** To evaluated the effect of simvastatin on bone mineral density (BMD) of the calcaneus in postmenopausal women with hyperlipidemia. **Methods** BMD of the calcaneus of 885 postmenopausal women with hyperlipidemia (TC>5.18 mmol/L or LDL-C>3.37 mmol/L) were studied. Simvastatin was used in these women. According to the T-score, normal bone mass, osteopenia, and osteoporosis were diagnosed. **Results** BMD of the calcaneus was 305.3 ± 59.2 mg/cm^2 before the treatment. The number of people with normal bone mass, osteopenia, and osteoporosis were 115, 446, and 324, respectively. After simvastatin administration (20 mg/d) for 3 months, the BMD was 309.7±56.3 mg/cm^2. The number of people with normal bone mass, osteopenia, and osteoporosis were 117, 459, and 319, respectively. After a 12-month treatment, BMD of the calcaneus was 312.5±60.9 mg/cm^2. The number of people with normal bone mass, osteopenia, and osteoporosis were 122, 460, and 303, respectively. **Conclusion** After a 12-month simvastatin (20 mg/kg·d) administration, BMD of the calcaneus increases in postmenopausal women with hyperlipidemia. It can not affect the risk of osteoporosis for these women.

Key words: Simvastatin; Postmenopausal; Hyperlipidemia; Bone mineral density

他汀类药物是竞争性 3-羟基-3-甲基戊二酰辅酶 A(HMG-CoA)还原酶的抑制剂,能够降低胆固醇生物合成、血清胆固醇浓度,进而降低心脏病的发生,目前临床上主要应用于血脂代谢异常疾病的治疗。1999 年,Mundy 等[1]首次发现包括辛伐他汀在内的他汀类药物可以增强 BMP-2 启动子活性,具有

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较强的促进骨形成的作用,随后辛伐他汀作为潜在的促骨形成药物成为骨组织工程学研究热点。

本研究通过对 885 例绝经后于体检时发现血脂代谢异常的女性进行了 1 年的观察分析,探讨辛伐他汀是否可以影响患者跟骨骨密度。

1 材料和方法

1.1 一般资料

本研究对象为 885 名临床体检时发现血脂异常(TC > 5.18 mmol/L 或 LDL-C > 3.37 mmol/L)的已绝经女性,年龄 45 ~ 70 岁,平均年龄 55 ± 10.3 岁。排除患有严重的肝肾疾患、甲状腺功能减退、内分泌疾患、类风湿关节炎等可能影响骨密度疾病。在研究过程中研究对象避免应用降钙素、双膦酸盐类或激素类等治疗骨质疏松的药物。治疗期间监测肝功能。

1.2 方法

本调查采用美国 GE 公司生产的 Achilles Express 超声骨密度仪(精确度误差为 2%),常规检查右足跟骨,按照世界卫生组织根据骨密度水平对于骨质疏松症的分级方式,分为骨质正常($T > -1SD$),骨质减少($-2.5SD \leqslant T \leqslant -1SD$),骨质疏松($T < -2.5SD$)。$T$ 值是患者的测量值与健康青年人平均值之差除以标准差所得的数值。并记录研究对象初始血脂水平。所有研究对象给予辛伐他汀 20 mg/d 治疗,并记录 3、12 月血脂水平及跟骨骨密度测定结果(德国罗氏全自动生化分析仪)。

1.3 统计学处理

结果采用 SPSS19.0 软件进行统计分析。跟骨骨密度测定定量资料,同时统计区分为骨质正常、骨量减少、骨质疏松的各类例数,采用卡方检验分析。$P < 0.05$ 为差异有统计学意义。

2 结果

辛伐他汀治疗前血脂(TC、LDL-C)水平为 7.68 ± 0.65 mmol/L、3.59 ± 0.82 mmol/L,治疗 3 月后血脂(TC、LDL-C)水平为 5.22 ± 0.75 mmol/L、2.35 ± 0.67 mmol/L,与治疗前相比差异具有显著性($P < 0.05$),治疗 12 月后血脂(TC、LDL-C)水平为 4.57 ± 0.61 mmol/L、1.52 ± 0.66 mmol/L,与治疗前相比差异具有显著性($P < 0.05$)。

辛伐他汀治疗前跟骨骨密度均值为 305.3 ± 59.2 mg/cm^2,口服辛伐他汀(20 mg/d)治疗 3 月后骨密度均值为 309.7 ± 56.3 mg/cm^2,与治疗前相比差异无统计学意义;12 月后跟骨骨密度均值为 312.5 ± 60.9 mg/cm^2,与治疗前相比差异具有统计学意义($P < 0.05$);治疗前、治疗 3 月、治疗 12 月后各组骨质正常、骨量减少、骨质疏松的平均骨密度相比差异不具有统计学意义($P > 0.05$)。

表 1 辛伐他汀治疗前后血脂(TC、LDL-C)水平、骨密度

Table 1 TC, LDL-C, and BMD before and after simvastatin treatment

时间	TC mmol/L	LDL-C mmol/L	骨密度 mg/cm^2
治疗前	7.68 ± 0.65	3.59 ± 0.82	305.3 ± 59.2
治疗 3 月	5.22 ± 0.75	2.35 ± 0.67	309.7 ± 56.3
治疗 12 月	4.57 ± 0.61	1.52 ± 0.66	312.5 ± 60.9

表 2 辛伐他汀治疗前后各组骨质正常、骨量减少、骨质疏松组的人数

Table 2 The number of people with normal bone mass, osteopenia, and osteoporosis before and after simvastatin treatment

时间	骨质正常	骨量减少	骨质疏松
治疗前	115	446	324
治疗 3 月	117	459	319
治疗 12 月	122	460	303

表 3 辛伐他汀治疗前后各组骨质正常、骨量减少、骨质疏松组的骨密度

Table 3 BMD in the normal bone mass, osteopenia, and osteoporosis group before and after simvastatin treatment

	骨质正常 mg/cm^2	骨量减少 mg/cm^2	骨质疏松 mg/cm^2
治疗前	383.1 ± 39.2	308.7 ± 48.2	214.1 ± 37.3
治疗 3 月	382.5 ± 41.5	309.1 ± 45.3	215.1 ± 40.3
治疗 12 月	385.3 ± 38.9	309.7 ± 47.4	214.7 ± 42.6

3 讨论

血脂代谢异常与骨质疏松症在临床上常常并发,因为无明显临床症状,而常常被忽略。Yamaguchi 等[2]认为绝经后妇女血脂水平与骨量以及骨脆性密切相关。Masse 等[3]认为绝经后妇女罹患骨质疏松症和心血管疾病的风险因素是共存的。目前临床上应用较广的降脂类药物为他汀类药物。辛伐他汀是竞争性 3-羟基-3-甲基戊二酰辅酶 A(HMG-CoA)还原酶的抑制剂,在临床中主要用于治疗血脂代谢异常,除了有降低胆固醇的作用外,还有改善内皮功能,增加 NO 的生物活性,稳定动脉硬化癍块等作用。1999 年 Mundy[1] 在筛选促骨生长化合物时发现辛伐他汀具有通过 BMP-2 途径促骨形

成的作用。

本研究选择了于体检时发现罹患血脂代谢异常并采用口服辛伐他汀的绝经后女性做为研究对象，同时检测跟骨骨密度。分析相关数据发现口服 3 个月辛伐他汀(20 mg/d)后血脂水平可以获得有效控制，跟骨骨密度均值增高，但是与初始时差异无统计学意义。口服 12 个月辛伐他汀(20 mg/d)后血脂均值降为正常值，跟骨骨密度与初始时差异显著，研究对象罹患骨质疏松的人数与未治疗前差异显著，这表明应用辛伐他汀(20 mg/d)治疗 12 个月血脂代谢异常的绝经后女性后跟骨骨密度增高，但不能降低这类人群骨质疏松患病风险降低。

目前在体外细胞实验研究中[1,4,5-21]，基本肯定了辛伐他汀的成骨潜能。但是在动物试验[7-45,17,18]对于辛伐他汀是否能够影响骨代谢、骨密度仍有争论。Mundy[1]、Oxlund[4]在动物试验中发现辛伐他汀在促进 OVX 大鼠骨形成增加密质骨骨密度的同时，抑制松质骨骨量的丢失。但是也有研究发现辛伐他汀不能阻止 OVX 大鼠的骨质疏松[23,24]。一些研究者[5,9-42]将辛伐他汀局部注射、包埋或者加入填充物，通过研究发现可以有效的促进骨形成、加速骨折愈合、加速骨缺损修复。或许辛伐他汀直接作用于细胞时更能诱导细胞的成骨潜能。

在临床上对于辛伐他汀是否具有促骨形成作用的研究[22-26]主要集中于对影响骨代谢的血清学指标以及骨密度的检测分析。Montagnani[23]和 Tikiz[24]研究发现辛伐他汀可以提高骨特异性碱性磷酸酶、骨钙蛋白等促骨代谢因子表达水平，对于骨吸收代谢的相关指标无影响，Rejnmark[25]发现应用 20 mg/d 辛伐他汀可以抑制骨转换，Rosenson[26]在研究中给予观察对象短期内大剂量辛伐他汀(80 mg/d)，发现辛伐他汀可以抑制骨转换率。Lupattelli[22]研究了 40 名服用 40 mg/d 辛伐他汀绝经后妇女 8～24 个月，认为服用 40 mg/d 辛伐他汀可以提高绝经后妇女的椎体、髋部骨密度，Montagnani[23]的研究得到了同样的结论：应用辛伐他汀 40 mg/d 12 个月发现绝经后妇女的椎体、髋部骨密度显著提高。但是 Tikiz[24]应用辛伐他汀治疗伴脂代谢异常的绝经后妇女 20 mg/d 12 个月后，发现绝经后妇女的椎体、髋部骨密度变化无统计学意义。在本研究中，观察对象应用辛伐他汀(20 mg/d)治疗 12 个月后跟骨骨密度变化显著。Uysal[27]通过对照研究认为辛伐他汀治疗后 2 型糖尿病患者的脊柱及髋部骨密度增高，与对照组相比差异无统计学意义。这些研究表明辛伐他汀可以影响骨代谢，但是具体机制仍不明确，影响骨代谢的相关因素需要进一步研究，如治疗时间、治疗剂量等。

同时影响骨密度的生活因素也有很多[28]，如年龄、生活习惯、饮食习惯、运动。本研究对象多数受过良好教育，在发现罹患骨质疏松、血脂代谢异常后，多数会改变饮食习惯，运动量加大，这会对患者的骨密度产生一定影响，干扰辛伐他汀对骨密度的影响分析。因此明确辛伐他汀对绝经后女性骨代谢的影响还需要大样本、长期的研究。

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