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·药物研究·

阿伦磷酸钠对绝经后 2 型糖尿病合并骨质疏松症患者骨代谢的影响

杨国花[1] 王亮[2*] 马远征[2] 张妍[2] 王文娇[2] 胡江伟[2] 李大伟[2] 陈琼[2] 马伟凤[2] 金毅[2] 杨帆[2]
1. 山西医科大学,太原 030001
2. 解放军 309 医院骨科中心,北京 100091

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摘要: 目的 探讨阿伦膦酸钠对绝经后 2 型糖尿病合并骨质疏松症患者骨代谢及骨密度的影响。**方法** 选择 2012 年 1 月至 2013 年 1 月在本院接受治疗的绝经后 2 型糖尿病合并骨质疏松症患者 51 例,给予阿伦膦酸钠治疗 6 个月。采用美国 Norland 双光能 X 线骨密度检测仪对所有患者进行腰椎 L_2-L_4 和左侧股骨近端(包括 Neck、Troch、Ward 三角区)骨密度测量,并测定身高、体重、空腹血糖(FBG)、HbAlc、PTH、OC、CTX、25(OH)VD、BALP 等。对比治疗前后骨密度及骨代谢标志物变化。**结果** 用阿伦膦酸钠治疗 6 个月使绝经后 2 型糖尿病合并骨质疏松症患者的 FBG、2hPG、HbA1c 降低,治疗前与治疗后相比较,差异有统计学意义($P<0.05$)。血 Ca、P 浓度治疗前与治疗后相比较,差异无统计学意义($P>0.05$)。骨代谢标志物 CTX 治疗前与治疗后相比,差异有统计学意义($P<0.05$)。OC、PTH、BALP、25OHVD 治疗前与治疗后相比较,差异无统计学意义($P>0.05$)。治疗前腰椎和股骨颈骨密度与治疗后相比较,差异有统计学意义($P<0.05$)。Torch、Ward 部位骨密度治疗前与治疗后相比较,差异没有统计学意义($P>0.05$)。**结论** 阿伦膦酸钠治疗绝经后 2 型糖尿病合并骨质疏松症疗效明显,短时间内可改善骨代谢指标和提高腰椎骨密度。

关键词: 绝经后妇女;2 型糖尿病;骨质疏松症; 阿伦磷酸钠

Effect of alendronate on bone metabolism in postmenopausal women with type 2 diabetes and osteoporosis

YANG Guohua[1], WANG Liang[2], MA Yuanzheng[2], ZHANG Yan[2], WANG Wenjiao[2], HU Jiangwei[2], LI Dawei[2], CHEN Qiong[2], MA Weifeng[2], JIN Yi[2], YANG Fan[2]
1. Shanxi Medical University, Taiyuan 030001
2. Orthopedic Center, the 309th Hospital of PLA, Beijing 100091, China
Corresponding author: WANG Liang, Email: wangl309@ sina. com

Abstract: Objective To investigate the effect of alendronate on bone metabolism and bone mineral density (BMD) in postmenopausal women with type 2 diabetes and osteoporosis. **Methods** Fifty-one postmenopausal women with type 2 diabetes and osteoporosis, who received treatment in our hospital from Janaury 2012 to Janaury 2013, were selected. All the patients were treated with alendronate for 6 months. BMD of L2 – L4 and the left proximal femur (including the neck, the Torch, and the Ward's triangle) was detected using dual energy X-ray absorptiometry (DEXA, Norland, USA). The height, weight, FBG, HbAlc, PTH, OC, CTX, 25(OH) VD, and BALP were also detected. The changes of BMD and bone metabolic markers before and after treatment were compared. **Results** In these postmenopausal women with type 2 diabetes and osteoporosis, after 6-month alendronate treatment, FBG, 2hPG and HbA1c were significantly lower than those before the treatment ($P<0.05$). The serum levels of Ca and P before the treatment had no significant difference with that after the treatment ($P>0.05$). The serum CTX level after the treatment was significant lower than that before the treatment ($P<0.05$). The serum levels of OC, PTH, BALP, and 25OHVD after the treatment had no significant difference with those before the treatment ($P>0.05$). BMD of L2, L3, L4, L2 – 4, the femoral neck after the treatment were significantly higher than that before the treatment ($P<0.05$). BMD of the Torch and the Ward's triangle after the treatment had no significant difference with that before the treatment ($P>0.05$). **Conclusion** The efficacy of alendronate on osteoporosis in postmenopausal with type 2 diabetes is obvious, which can improve the bone metabolic markers and BMD in a short time.

Key words: Postmenopausal women; Type 2 diabetes; Osteoporosis; Alendronate

*通讯作者: 王亮,Email:wangl309@ sina. com

随着社会的发展和人口的老龄化,糖尿病(diabetes mellitus,DM)在世界范围内的发病率呈增高趋势,其急慢性并发症严重危害人类健康。糖尿病性骨质疏松症(diabetic osteoporosis,DOP)是糖尿病在骨骼系统出现的严重并发症,并成为长期疼痛和功能障碍的主要原因。骨质疏松症(Osteoporosis,OP)是一种以骨量低下,骨微结构破坏,导致骨脆性增加,易发生骨折为特征的全身性骨病[1]。绝经后女性由于卵巢功能减退,雌激素水平下降,骨量丢失加速,是骨质疏松症的高发人群。伴有糖尿病的患者则进一步增加了骨质疏松性骨折的风险。当出现骨折时,会给患者及家庭带来严重的后果,并有很高的致死率和致残率。因此积极有效地治疗糖尿病性骨质疏松具有重要的临床意义。本研究选取本院 51 例糖尿病合并骨质疏松症患者,给予阿伦膦酸钠治疗 6 个月,观察治疗前后的临床效果。

1 材料和方法

1.1 研究对象

本研究中选取 2012.01 ~ 2013.01 在我院住院的绝经后 2 型糖尿病合并骨质疏松症患者 51 例,平均年龄 68.38 ± 4.13 岁,所有入选对象均无肝、肾功能异常、甲状腺、甲状旁腺、血液系统疾病、结缔组织疾病等,近期无服用钙剂、VitD 及糖皮质激素史。

1.2 诊断标准

骨质疏松症的诊断:参照 1994 年 WHO 推荐的诊断方法[1],测得的骨密度与同性别峰值骨密度相比,其骨密度下降标准差,如有 1 个或 1 个以上部位 T 值 ≤ −2.5SD 为骨质疏松;−2.5SD < T 值 ≤ −1SD 为骨量减少;T 值 > −1SD 为正常骨量。2 型糖尿病诊断:根据世界卫生组织(WHO)1999 年糖尿病诊断标准[2]:空腹血糖(FBG)≥7.0 mmol/L;口服葡萄糖耐量试验(OGTT)服糖后 2 h 血糖≥11.1 mmol/L 者即确定为糖尿病。

1.3 研究方法

1.3.1 一般情况:所有研究对象填写调查表,包括年龄,性别、身高、体重、BMI 等,并录入数据库。入选后对所有患者进行健康教育,量化饮食和运动,合理膳食,多晒太阳,强化降糖治疗,合理补充胰岛素。

1.3.2 治疗用药:所有患者正常服用降血糖药物或注射胰岛素保持血糖浓度基本正常,同时给予治疗骨质疏松的药物——阿伦膦酸钠(福善美,默沙东公司)。口服,每周 1 次,每次 1 片(70 mg),清晨空腹以温开水送服,服药后 30 min 内或当日进食前避免躺卧,以免引起食管等上消化道不良反应。所有患者服药前检测血钙浓度,对于低钙血症的患者给予补充钙剂。

1.3.3 血生化指标及骨代谢指标测定:所有研究对象于清晨空腹抽静脉血,测定空腹血糖(FBG)、HbAlc、甘油三酯(TG)、胆固醇(TC)、HDL-C、LDL-C,应用日立牌全自动生化分析仪检测患者的血钙、血磷浓度。美国 Thermo 公司酶标免疫分析仪检测甲状旁腺素(PTH)、骨钙素(OC)、Ⅰ型胶原 C 端肽(CTX)、25(OH)VD、骨特异性碱性磷酸酶(BALP)。

1.3.4 双能 X 线骨密度检测:分别于服药前,服药 6 个月时,采用美国 Norland 公司生产的 XR-46 双光能 X 线骨密度检测仪,测定腰椎 L_{2-4}、Neck、Ward 三角区、Troch 的骨密度。该方法测定人体骨密度的精密度变异系数为 1%。对比治疗前后各部位骨密度的变化情况。

1.4 统计学处理

所有数据采用 SPSS 13.0 软件进行数据统计分析,计量资料均用 $\bar{x} \pm s$ 表示,组间比较采用 t 检验,以 $P < 0.05$ 具有统计学意义。

2 结果

2.1 一般情况

本研究共入组 51 例女性,患者年龄 68.38 ± 4.13,BMI 24.63 ± 3.6 kg/m^2,E2 0.14 ± 0.13nmol/L,空腹血糖(FBG)8.61 ± 0.31 nmol/L,糖化血红蛋白 7.68 ± 0.76%.,TG1.80 ± 0.74m mol/L,TC 5.12 ± 1.16m mol/L,HDL-C 1.34 ± 0.28m mol/L,LDL-C 2.72 ± 0.90m mol/L。

2.2 生化指标及骨代谢指标比较

分别于开始治疗前、治疗 6 个月测定血生化指标,结果显示治疗后较治疗前 FBG、2hPG、HbA1c 水平明显降低,差异具有统计学意义($P < 0.05$),血 Ca、血 P 变化无统计学意义($P > 0.05$)。见表 1。

2.3 骨代谢指标改变情况

骨代谢标志物中,治疗前后 CTX 降低差异具有统计学意义($P < 0.05$),骨钙素 OC、PTH、25OHVD、BALP 变化无统计学差异($P > 0.05$)。

2.4 双光能 X 线骨密度比较

治疗后 Ward 三角区、Troch 骨密度与治疗前比较无明显统计学差异($P > 0.05$),两组腰椎(L_2-L_4)和股骨颈(Neck)骨密度变化有显著统计学差异($P < 0.05$)。见表 3。

表 1 血生化指标比较

Table 1 Comparison of serum biochemical indexes

组别	FBG(m mol/L)	2hPG(m mol/L)	HbA1c(%)	血 Ca(n mol/L)	血 P(n mol/L)
治疗前	8.61 ±0.31	10.57 ±0.61	7.68 ±0.76	2.20 ±0.12	1.12 ±0.35
治疗后	7.25 ±0.37	8.06 ±3.21	6.12 ±0.51	2.30 ±0.39	1.14 ±0.15

注:血 Ca、血 P 与治疗前相比,$P>0.05$; FBG、2hPG、HbA1c 与治疗前相比,$P<0.05$

表 2 骨转化标志物变化

Table 2 Changes of bone metabolic markers

组别	PTH(pmol/L)	OC(μg/L)	CTX(μg/L)	BALP(U/L)	25(OH)VD(ng/mL)
治疗前	26.95 ±6.81	6.12 ±1.67	0.39 ±0.08	68.6 ±10.5	18.22 ±12.04
治疗后	28.72 ±8.73	6.03 ±1.57	0.18 ±0.06	66.7 ±8.60	22.62 ±13.69

注:OC、PTH、25(OH)VD、BALP 与治疗前相比,$P>0.05$;CTX 与对治疗前相比,$P<0.05$

表 3 BMD 结果比较(g/cm^2)

Table 3 SComparison of BMD (g/cm^2)

组别	L_2	L_3	L_4	L_{2-4}	Neck	Torch	Ward
治疗前	0.73 ±0.10	0.69 ±0.13	0.74 ±0.13	0.75 ±0.11	0.65 ±0.13	0.57 ±0.14	0.48 ±0.13
治疗后	0.77 ±0.11	0.74 ±0.14	0.79 ±0.12	0.79 ±0.32	0.69 ±0.12	0.59 ±0.37	0.50 ±0.12

注:Troch、Ward 区与治疗前相比,$P>0.05$;L_2、L_3、L_4、L_{2-4}、Neck 部位与治疗前相比,$P<0.05$

3 讨论

糖尿病是现代常见的疾病,据世界卫生组织 2012 年 9 月报告,全球有 3.47 亿人患有糖尿病,其中约有 90% 为 2 型糖尿病(T2DM)。一些研究发现,糖尿病患者因饮食的限制,导致骨生长所需要的营养物质及多种微量元素的缺乏,长期将会导致骨质疏松症。糖尿病患者的长期高血糖状态可致渗透性利尿,使尿钙、磷排泄增加,刺激甲状旁腺素分泌增加,溶骨作用增强,加速了骨质疏松的发展[4,5]。当糖尿病患者胰岛素缺乏或胰岛素敏感性下降时,会影响骨胶原的合成,导致骨基质分解,钙盐流失,可引起骨质疏松症。另外,胰岛素不足、糖基化终末产物以及糖尿病的并发症都会对骨产生不利的影响,并且随着病程延长,糖尿病患者骨质疏松症的发病率也越来越高。Lecka-Czernik 等[6]研究表明,由于肥胖、糖尿病并发症、年龄、糖尿病病程、以及糖尿病的治疗药物等因素,会影响 2 型糖尿病患者皮质骨质量,导致骨强度降低。2 型糖尿病患者的骨折风险往往增加,这与糖尿病周围神经病变导致平衡能力差及糖尿病视网膜病变导致视力下降等导致跌倒风险增加有关的因素有关。

双膦酸盐类药物预防和治疗骨质疏松的作用在临床上已经确立[7],阿仑膦酸钠(福善美)是一种氨基双膦酸盐类药物,与羟基磷灰石有极强亲和力,能够沉积于骨骼,抑制破骨细胞活性,是对破骨细胞介导的骨质再吸收的一种有效的特异性抑制剂,它不仅可以抑制破骨细胞的活性,也促进破骨细胞凋亡,减少骨吸收和减慢骨量丢失的速度[8,9]。国内外研究表明,应用双膦酸盐类药物可使骨密度和骨代谢指标均得到明显改善[10]。孟讯吾等[11]研究发现,予 274 例绝经后骨质疏松患者每日口服 10mg 阿伦膦酸钠及元素钙 500mg,治疗 6 个月后,患者腰椎、股骨颈、ward 三角区大转子部位骨密度均显著增加。也有研究发现[12],阿伦膦酸钠联合钙尔奇 D 可明显提高老年女性糖尿病骨质疏松患者的 BMD 和改善骨的代谢指标。与文献结果一致,我们的研究显示阿伦磷酸钠治疗半年可使绝经后 2 型糖尿病合并骨质疏松患者的腰椎 2-4、股骨颈骨密度明显增加,同时改善骨的代谢指标。

综上所述,阿伦膦酸钠治疗绝经后 2 型糖尿病合并骨质疏松症效果显著,可增加骨密度,降低骨转化水平,降低骨折发生率。然而在 10 年骨折风险评估(FRAX)中尚不包括糖尿病,因此 FRAX 往往低估了此类患者的骨折风险,临床医师在使用 FRAX 时必须注意这一情况。因为糖尿病患者有较高的骨折风险,骨折又大大增加老年人的病残率和死亡率,不但给患者带来痛苦和经济负担,也会给医疗资源带来很大压力。因此,糖尿病患者更需要关注骨骼健康,控制血糖的同时,积极防治骨质疏松症,降低骨折的发生率[13]。

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