

· 论著 ·

# 唑来膦酸对慢性阻塞性肺疾病患者骨质疏松症的临床疗效及对OPG/RANK/RANKL系统的影响

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**【摘要】目的** 探讨唑来膦酸对慢性阻塞性肺疾病患者骨质疏松症的临床疗效及对OPG/RANK/RANKL系统的影响。**方法** 选取2019年5月~2022年9月在本院就诊的慢性阻塞性肺疾病合并骨质疏松症患者86例,在慢阻肺规范化治疗基础上,予以钙尔奇D,同时采用静脉注射的方式予以唑来膦酸注射液。统计患者治疗前后视觉模拟评分法(visual analogue scale, VAS)评分、骨密度、肺功能、骨代谢指标及相关性分析骨代谢指标关系。**结果** 治疗后VAS评分显著低于治疗前,腰椎BMD、股骨颈BMD均显著高于治疗前,差异均具有统计学意义( $t=57.527$ ,  $P<0.001$ ;  $t=3.039$ ,  $P=0.004$ ;  $t=8.012$ ,  $P<0.001$ )。治疗后肺功能FEV1、FEV1/FVC均优于治疗前,差异具有统计学意义( $t=3.009$ ,  $P=0.004$ ;  $t=2.321$ ,  $P=0.025$ )。治疗后骨代谢指标RANKL、RANKL/OPG、PINP、S-CTX、血磷均低于治疗前,差异均具有统计学意义( $P<0.05$ ),治疗前后OPG、血钙水平比较,差异无统计学意义( $P>0.05$ )。相关性分析显示,OPG均与PINP、S-CTX呈负相关,但无显著差异( $P>0.05$ ),RANKL、RANKL/OPG均与PINP呈正相关,但无显著差异( $P>0.05$ ),但与S-CTX呈正相关,具有统计学意义( $P<0.05$ )。**结论** 唑来膦酸用于治疗慢性阻塞性肺疾病合并骨质疏松症患者,可改善患者骨代谢,提高骨密度,其治疗机制与介导OPG/RANK/RANKL系统有关。

**【关键词】** 唑来膦酸; 慢性阻塞性肺疾病; 骨质疏松症; 临床疗效; OPG/RANK/RANKL系统

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## Clinical Effect of Zoledronic Acid on Osteoporosis in Patients with Chronic Obstructive Pulmonary Disease and Its Effect on OPG/RANK/RANKL System

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**Abstract: Objective** To investigate the clinical effect of zoledronic acid on osteoporosis in patients with chronic obstructive pulmonary disease and the effect on OPG/RANK/RANKL system. **Methods** A total of 86 patients with chronic obstructive pulmonary disease combined with osteoporosis admitted to our hospital from May 2019 to September 2022 were selected. On the basis of standardized treatment of COPD, calcini D was given and zoledronic acid injection was given intravenously. Visual Analogue Scale (VAS) scores, bone mineral density, lung function and bone metabolism indexes were analyzed before and after treatment, and their correlations were analyzed. **Results** VAS score after treatment was significantly lower than before treatment, BMD of lumbar spine and femoral neck were significantly higher than before treatment, the differences were statistically significant ( $t=57.527$ ,  $P<0.001$ ;  $t=3.039$ ,  $P=0.004$ ;  $t=8.012$ ,  $P<0.001$ ). Both FEV1 and FEV1/FVC were better after treatment than before, and the difference was statistically significant ( $t=3.009$ ,  $P=0.004$ ;  $t=2.321$ ,  $P=0.025$ ). After treatment, bone metabolism indexes RANKL, RANKL/OPG, PINP, S-CTX and blood phosphorus were all lower than before treatment, with statistical significance ( $P<0.05$ ), while OPG and blood calcium levels before and after treatment had no statistical significance ( $P>0.05$ ). Correlation analysis showed that OPG was negatively correlated with PINP and S-CTX, but there was no significant difference ( $P>0.05$ ); RANKL and RANKL/OPG were positively correlated with PINP, but there was no significant difference ( $P>0.05$ ), but they were positively correlated with S-CTX, with statistical significance ( $P<0.05$ ). **Conclusions** Zoledronic acid can improve bone metabolism and bone mineral density in patients with chronic obstructive pulmonary disease complicated with osteoporosis, and its therapeutic mechanism is related to mediating OPG/RANK/RANKL system.

**Keywords:** Zoledronic Acid; Chronic Obstructive Pulmonary Disease; Osteoporosis; Clinical Effect; OPG/RANK/RANKL System

慢性阻塞性肺疾病属于临床上常见的呼吸系统类疾病,主要特征为气流受限及呼吸道症状<sup>[1]</sup>。此类疾病表现为进行性发展的慢性呼吸系统疾病,易导致机体脏器功能长时间处于供氧不足的状态<sup>[2]</sup>。近年来,因我国正处于人口老龄化社会,骨质疏松发生率呈现明显上升趋势<sup>[3]</sup>。相关研究显示<sup>[4]</sup>,50岁以上人群中,其中20%为男性患有骨质疏松,30%女性患有骨质疏松。近年来,有研究报道<sup>[5]</sup>,慢性阻塞性肺疾病与骨质疏松具有关系。研究报道<sup>[6]</sup>,慢性阻塞性肺疾病患者发生骨质疏松风险大,慢性阻塞性肺疾病合并骨质疏松发生率最高可达到60%。骨折为骨质疏松症常见并发症之一,具有发病率高、死亡率高及致残率高等特点,且此类患者治疗周期长,增加患者经济压力,还影响患者日常生活和工作<sup>[7-8]</sup>。由此,积极寻找有效治疗方案改善慢性阻塞性肺疾病患者骨代谢,预防骨折具有重要意义。唑来膦酸属于一类新型

药物,常用于治疗骨质疏松症,主要通过正向激活成骨细胞,逆向抑制破骨细胞,避免骨头受到破坏,进而维持骨量,最终改善骨质疏松<sup>[9]</sup>。且唑来膦酸周期长,一年仅需注射1次,依从性好<sup>[10]</sup>。本次研究主要探讨唑来膦酸对慢性阻塞性肺疾病患者骨质疏松症的效果,现将内容报道如下。

### 1 资料与方法

**1.1 一般资料** 选取2019年5月~2022年9月在本院就诊的慢性阻塞性肺疾病合并骨质疏松症患者86例,其中男性患者人数为50例,女性患者人数为36例,年龄分布范围为55~80岁,平均年龄( $67.45 \pm 12.21$ )岁,平均身高( $1.67 \pm 0.13$ )cm,平均体重( $67.7 \pm 14.5$ )kg。

纳入标准:符合中华医学会呼吸病学分会慢性阻塞性肺疾病

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学组制定的《慢性阻塞性肺疾病诊治指南(2021年修订版)》中关于慢性阻塞性肺疾病诊断标准<sup>[11]</sup>；②符合中华医学会骨质疏松和骨矿盐疾病分会制定的《原发性骨质疏松症诊疗指南(2017)》中关于骨质疏松症诊断标准<sup>[12]</sup>，且均经过影像学及骨密度检查证实；③患者存在不同程度自发性周身疼痛；④既往无抗骨质疏松药物治疗史。排除标准：①合并心、肝、肾等重要脏器功能障碍；②合并原发性甲状旁腺功能亢进、风湿性疾病等；③对本研究药物过敏者；④中途退出本次研究；⑤正在参与其他临床研究。

**1.2 研究方法** 在慢阻肺规范化治疗基础上，予以钙尔奇D(生产厂家：惠氏制药有限公司，批准文号：国药准字H10950029，规格：每片含钙600毫克/维生素D3125国际单位)，每次用药剂量600mg，每天2次，连续干预1年。同时采用静脉注射的方式予以唑来膦酸注射液(生产厂家：正大天晴药业集团股份有限公司，批准文号：国药准字H20113138，规格：100mL)，用药剂量为5mg，每年用药1次。

**1.3 观察指标** 统计患者治疗前后视觉模拟评分法(Visual Analogue Scale, VAS)评分、骨密度、肺功能、骨代谢指标及相关性分析骨代谢指标关系。①VAS评分<sup>[13]</sup>，主要用于评估患者疼痛程度，分值范围为0至10分，分数越高说明患者疼痛程度越强。②骨密度，采用双能X线骨密度仪检测腰椎、股骨颈BMD。③肺功能，采用肺功能检测仪检测最大呼气流量(Peak Expiratory Flow, PEF)、1s用力呼气容积(Forced Expiratory Volume in One Second, FEV1)、FEV1占预计值百分比(FEV1%)。④骨代谢指标，包括骨保护蛋白(Osteoprotegerin, OPG)、核因子- $\kappa$ 受体活化因子配体(Receptor Activator of Nuclear factor  $\kappa$ B Ligand, RANKL)、RANKL/OPG、I型前胶原氨基端前肽(Procollagen type I N-terminal Peptide, PINP)、I型胶原交联C-末端肽(C-telopeptide of type I collagen, S-CTX)、血钙、血磷，采用全自动生化检测仪检测血钙、血磷水平，采用酶联免疫吸附试验检测血清OPG、ANKL、S-CTX水平，采用电化学发光法检测PINP水平。

**1.4 统计学方法** 将本次研究中所涉及到的两组病人的数据均录入到SPSS 25.0软件中，针对两组中的计量资料进行表述时，通过t值对检验结果进行检验，通过 $(\bar{x} \pm s)$ 进行，对于计数资料进行表述，通过 $\chi^2$ 对结果获取，当 $P < 0.05$ 表明存在显著性差异。

2 结果

**2.1 患者治疗前后VAS评分、骨密度差异性观察** 治疗后VAS评分显著低于治疗前，腰椎BMD、股骨颈BMD均显著高于治疗前，差异均具有统计学意义( $t=57.527$ ,  $P < 0.001$ ;  $t=3.039$ ,  $P=0.004$ ;  $t=8.012$ ,  $P < 0.001$ )。具体内容见表1。

**2.2 患者治疗前后肺功能差异性观察** 治疗后肺功能FEV1、FEV1/FVC均优于治疗前，差异具有统计学意义( $t=3.009$ ,  $P=0.004$ ;  $t=2.321$ ,  $P=0.025$ )。具体内容见表2。

**2.3 患者治疗前后骨代谢指标差异性观察** 治疗后骨代谢指标RANKL、RANKL/OPG、PINP、S-CTX、血磷均低于治疗前，差异均具有统计学意义( $P < 0.05$ )，治疗前后OPG、血钙水平比较，差异无统计学意义( $P > 0.05$ )。具体内容见表3。

**2.4 相关性分析骨代谢指标关系** 相关性分析显示，OPG均与PINP、S-CTX呈负相关，但无显著差异( $P > 0.05$ )，RANKL、RANKL/OPG均与PINP呈正相关，但无显著差异( $P > 0.05$ )，但与S-CTX呈正相关，具有统计学意义( $P < 0.05$ )。具体内容见表4。

**2.5 安全性分析** 治疗期间，3例发热，1例头痛，经过对症治疗后均明显好转。

表1 患者治疗前后VAS评分、骨密度差异性观察

| 时间  | 例数 | VAS评分(分)        | 腰椎BMD(g/cm <sup>2</sup> ) | 股骨颈BMD(g/cm <sup>2</sup> ) |
|-----|----|-----------------|---------------------------|----------------------------|
| 治疗前 | 43 | 7.16 $\pm$ 0.28 | 0.69 $\pm$ 0.15           | 0.62 $\pm$ 0.08            |
| 治疗后 | 43 | 3.94 $\pm$ 0.19 | 0.77 $\pm$ 0.12           | 0.72 $\pm$ 0.07            |
| t   |    | 57.527          | 3.039                     | 8.012                      |
| P   |    | <0.001          | 0.004                     | <0.001                     |

表2 患者治疗前后肺功能差异性观察

| 时间  | 例数 | PEF(L/s)        | FEV1(%)           | FEV1/FVC(%)       |
|-----|----|-----------------|-------------------|-------------------|
| 治疗前 | 43 | 7.42 $\pm$ 1.02 | 45.11 $\pm$ 18.20 | 53.32 $\pm$ 7.02  |
| 治疗后 | 43 | 7.76 $\pm$ 1.11 | 55.13 $\pm$ 15.35 | 58.01 $\pm$ 10.01 |
| t   |    | 1.317           | 3.009             | 2.321             |
| P   |    | 0.195           | 0.004             | 0.025             |

表3 患者治疗前后骨代谢指标差异性观察

| 时间  | 例数 | OPG(pg/mL)         | RANKL(pg/mL)       | RANKL/OPG       | PINP(ng/mL)     | S-CTX(pg/mL)       | 血钙(mmol/L)      | 血磷(mmol/L)      |
|-----|----|--------------------|--------------------|-----------------|-----------------|--------------------|-----------------|-----------------|
| 治疗前 | 43 | 244.01 $\pm$ 85.12 | 534.65 $\pm$ 88.01 | 2.17 $\pm$ 0.23 | 7.62 $\pm$ 2.91 | 335.08 $\pm$ 59.12 | 2.11 $\pm$ 0.16 | 1.29 $\pm$ 0.09 |
| 治疗后 | 43 | 265.32 $\pm$ 90.32 | 408.13 $\pm$ 53.05 | 1.61 $\pm$ 0.14 | 5.32 $\pm$ 2.51 | 107.13 $\pm$ 24.09 | 2.17 $\pm$ 0.24 | 1.21 $\pm$ 0.18 |
| t   |    | 1.046              | 7.939              | 14.479          | 3.680           | 22.761             | 1.340           | 2.494           |
| P   |    | 0.301              | <0.001             | <0.001          | 0.001           | <0.001             | 0.188           | 0.017           |

表4 相关性分析骨代谢指标关系

| 指标        | PINP   |       | S-CTX  |       |
|-----------|--------|-------|--------|-------|
|           | r      | P     | r      | P     |
| OPG       | -0.331 | 0.542 | -0.161 | 0.438 |
| RANKL     | 0.449  | 0.157 | 0.472  | 0.003 |
| RANKL/OPG | 0.373  | 0.267 | 0.341  | 0.039 |

3 讨论

骨质疏松症属于慢性阻塞性肺疾病患者常见的并发症，其发生主要与机体运动功能下降、机体内缺氧存在关系<sup>[14-15]</sup>。研究称<sup>[16]</sup>，慢性阻塞性肺疾病患者往往伴有体重下降，导致机体负荷减少，骨形成下降，骨密度下降，发生骨质疏松症风险性增加。老年慢性阻塞性肺疾病合并骨质疏松症患者，需要长时间卧床，因

此，发生褥疮、肺部感染等并发症风险高，严重影响患者生活质量，甚至生命安全<sup>[17]</sup>。积极提高慢性阻塞性肺疾病骨密度尤为重要。

临床上用于治疗骨质疏松症患者的药物主要包括骨吸收抑制剂、骨形成促进剂<sup>[18]</sup>。双膦酸盐类属于常见的骨吸收抑制剂，可有效抑制破骨细胞介导的骨吸收，最终增加骨密度<sup>[19]</sup>。唑来膦酸

具有较强的吸附力,药物脱落率低,且少量脱落下来的药物可经强大吸附力被重新吸收<sup>[20]</sup>。本次研究结果显示,治疗后患者骨代谢指标以及骨密度均显著优于治疗前,此项结果表明唑来膦酸能够有效提高骨代谢,改善骨密度。且治疗后VAS评分显著低于治疗前,表明唑来膦酸还可缓解慢性阻塞性肺疾病合并骨质疏松症患者疼痛程度。与目前相关研究报道具有一致性<sup>[21]</sup>。

相关研究报道<sup>[22]</sup>,慢性阻塞性肺疾病本质属于一类以气道炎症为核心的全身性炎症反应,炎性因子如IL-6、IL-1 $\beta$ 、TNF- $\alpha$ 等对OPG/RANK/RANKL系统发挥作用,诱导RANKL表达上升,进一步激活NF- $\kappa$ B信号通路,最终促进破骨细胞分化程度。又有研究称<sup>[23]</sup>,OPG/RANK/RANKL系统在慢性阻塞性肺疾病骨量丢失中具有关键作用。又有研究报道<sup>[24]</sup>,RANKL、RANKL/OPG水平在慢性阻塞性肺疾病中表达均明显上升。一项基础实验表明<sup>[25]</sup>,唑来膦酸可以通过抑制RANKL介导的NF- $\kappa$ B信号通路,进而对破骨细胞分化、骨吸收过程发挥抑制作用。本次研究结果显示,治疗后RANKL、RANKL/OPG均优于治疗前,表明唑来膦酸发挥作用与介导OPG/RANK/RANKL系统有关。且本研究结果还发现,患者经唑来膦酸治疗后,不良反应轻微,经对症治疗明显好转。这一结果与目前研究报道具有一致性<sup>[26]</sup>。

综上所述,唑来膦酸用于治疗慢性阻塞性肺疾病合并骨质疏松症患者,可改善患者骨代谢,提高骨密度,其治疗机制与介导OPG/RANK/RANKL系统有关。

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