

• 论著 •

## 绝经后类风湿关节炎女性骨吸收与放射学进展相关

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**摘要:** 目的 探讨绝经后类风湿关节炎(rheumatoid arthritis, RA)患者骨代谢指标与疾病活动指标、骨矿物质密度(bone mineral density, BMD)和放射学进展的相互关系。方法 本研究共募集了68例绝经后RA患者。血清检测指标包括红细胞沉降率(ESR)、C反应蛋白(CRP)、类风湿因子(RF)和抗环瓜氨酸肽抗体(CCP)。同时检测了钙、维生素D、骨碱性磷酸酶(BAP)和β胶原特殊序列(β-crosslaps)的水平。采用双能X线骨吸收仪(DXA)测量腰椎和左股骨颈的BMD(g/cm<sup>2</sup>)。DAS28和Sharp评分分别用于计算疾病活动度和放射学进展评估。运用Spearman相关分析对临床血清标记和疾病指标的相关性进行分析。结果 纳入患者的异常BMD比率为94.12%,其中29.41%(20/68)为骨量减少,而64.71%(44/68)为骨质疏松。ESR、CRP和DAS28之间显著相关( $P < 0.05$ ),均提示疾病活动。血清β-crosslaps水平与任一疾病活动指标均无相关性( $P$ 均 $> 0.05$ ),但与Sharp评分呈正相关( $r = 0.776$ ,  $P = 1 \times 10^{-6}$ )。结论 绝经后RA患者骨量减少及骨质疏松现象突出,可能与疾病活动和/或关节结构破坏有关。β-crosslaps是与放射学进展相关而与疾病活动无关的有价值的血清标记。

**关键词:** 类风湿关节炎;骨形成;骨吸收;骨量减少;骨质疏松;绝经后

### Bone resorption was correlated with radiologic progression in postmenopausal women with rheumatoid arthritis

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**Abstract: Objectives** To determine the levels of bone turnover markers in patients with rheumatoid arthritis (RA) and the correlation with disease activity index, bone mineral density (BMD), and radiographic progression. **Methods** Sixty-eight postmenopausal women with RA were recruited in our study. Serologic measurement including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) were analyzed. Calcium, vitamin D, bone alkaline phosphatase (BAP) β-crosslaps were also detected. Bone mineral density (BMD, g/cm<sup>2</sup>) of the lumbar spine and the left femoral neck was measured using dual-energy X-ray absorptiometry (DXA). DAS28 and Sharp score were separately calculated for disease activity and radiographic progression evaluation. Spearman correlation analysis was conducted between clinical biomarkers and disease indexes. **Results** The overall rate of patient with abnormal BMD was 94.12%, with 29.41% (20/68) of osteopenia and 64.71% (44/68) of osteoporosis, respectively. ESR, CRP, and DAS28 were significantly correlated with each other showing consistent disease activity ( $P < 0.05$ ). Serum β-crosslaps level ( $452.87 \pm 202.40$  ug/l) was not correlated with any of disease activity markers (all  $P > 0.05$ ) but was positively correlated with Sharp score ( $150.76 \pm 59.71$ ) in postmenopausal women with RA ( $r = 0.776$ ,  $P = 1 \times 10^{-6}$ ). **Conclusion** Osteopenia and osteoporosis are predominant in RA which might be related to disease activity and/or structural damage. β-crosslaps implies radiographic progression instead of disease

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activity.

**Key words:** Rheumatoid arthritis; Bone formation; Bone resorption; Osteopenia; Osteoporosis; Postmenopausal

类风湿关节炎 (rheumatoid arthritis, RA) 患者骨量减少和骨质疏松的发生率高于同年龄性别健康对照。RA 的关节炎症可诱发局部的手关节周围的骨质疏松,而手部的骨量丢失与全身的骨质疏松密切相关<sup>[1]</sup>。研究表明,许多因素参与 RA 的骨量减少,性激素<sup>[2]</sup>、糖皮质激素<sup>[3]</sup>和低血清 25OHD 水平<sup>[4]</sup>均与低 BMD 相关。本研究旨在探索可预测放射学进展并可用于病情监测和治疗疗效评判的血清学指标。

## 1 资料与方法

### 1.1 研究对象

本研究选取 2013 年 10 月–2015 年 12 月在我院住院的 68 例绝经后 RA 患者。入组病例接受改善病情抗风湿病药 (disease modifying anti-rheumatic drugs, DMARDs) 或生物制剂治疗,联合或不联合非甾体抗炎药 (non-steroidal anti-inflammatory drugs, NSAIDs) 和小剂量口服激素。所有患者均拍摄双手正位片。采用疾病活动度评分 (Disease Activity Score, DAS 28) 评估病情活动。RA 患者均符合 2010 年 ACR 分类标准<sup>[5]</sup>。

### 1.2 方法

**1.2.1 血清学标记测定:** 红细胞沉降率 (erythrocyte sedimentation rate, ESR; 0~20 mm/h), C 反应蛋白 (C-reactive protein, CRP; 0~10 mg/l), 类风湿因子 (rheumatoid factor, RF; 0~14 IU/ml) 和抗环瓜氨酸肽抗体 (anti-cyclic citrullinated peptid, anti-CCP; 0~17 U/ml) 采用酶联免疫法检测。钙和骨碱性磷酸酶 (bone alkaline phosphatase, BAP) 采用 ELISA (Beckman, USA) 检测。Elecsys Beta-crosslap (113~1008 ug/l) 和维生素 D 采用电子化学免疫发光法 (ECLIA) (Cobas, Roche, Germany) 检测。

**1.2.2 放射学评估:** RA 的放射学严重性通过 Sharp 评分进行评估,包括关节间隙变窄和侵蚀评分<sup>[6]</sup>。Sharp 关节间隙变窄评分评估 36 个手关节 (总分: 144 分); Sharp 侵蚀评分评估 34 个手关节 (总分: 170 分)。

**1.2.3 骨量评估:** 采用双能 X 线骨吸收仪 (DXA) 检测腰椎 (腰 1–腰 4 椎体,前后位) 和左股骨头的 BMD (g/cm<sup>2</sup>) 值和根据正常平均年轻健康成人的标准差计算 T 值。根据世界卫生组织 (WHO) 定义: T

值在 -1 和 -2.5 之间为骨量减少, T 值小于等于 -2.5 为骨质疏松。FRAX 工具计算骨折风险和髌骨折风险。

### 1.3 统计学分析

采用 SPSS 13.0 进行统计学分析。所有的结果以  $\bar{x} \pm s$  表示。通过 Spearman's 等级相关分析检验血清标记与临床指标的相关性。P < 0.05 具有统计学意义。

## 2 结果

**2.1** 68 例 RA 患者均为绝经后女性,研究对象临床资料见表 1。

表 1 入组患者的基本资料

Table 1 Characterization of the study cohort

| 指标                                 | RA 患者 (n=68)    |
|------------------------------------|-----------------|
| 年龄 (岁)<br>Age (years)              | 64.16 ± 9.92    |
| 病程 (年)<br>Disease duration (years) | 15.05 ± 11.53   |
| 红细胞沉降率 (毫升/h)<br>ESR (mm/hour)     | 56.44 ± 39.18   |
| C 反应蛋白 (mg/L)<br>CRP (mg/L)        | 38.70 ± 56.28   |
| 类风湿因子 (IU/ml)<br>RF (IU/ml)        | 235.38 ± 373.26 |
| 抗环瓜氨酸肽抗体 (RU/ml)<br>CCP (RU/ml)    | 371.11 ± 596.49 |
| 疾病活动度评分<br>DAS28                   | 5.52 ± 1.93     |

### 2.2 血清学标记、BMD 值和放射学评分

68 例 RA 患者的血清学标记, BMD 值和放射学评分见表 2。骨量减少和骨质疏松比率分别为 29.41% (20/68) 和 64.71% (44/68)。骨量异常的总比率为 94.12%。仅有 4 例患者 (5.88%) 骨量正常。

### 2.3 相关性分析

在配对相关分析中,年龄与髌 BMD ( $r = -0.388$ ,  $P = 0.001$ ) 和髌 T 值 ( $r = -0.412$ ,  $P = 0.0005$ ) 呈负相关,与骨折风险 ( $r = 0.335$ ,  $P = 0.005$ ) 和髌骨折风险 ( $r = 0.429$ ,  $P = 2.61 \times 10^{-4}$ ) 呈正相关。年龄和腰 BMD ( $r = -0.217$ ,  $P = 0.076$ ) 及腰 T 值 ( $r = -0.197$ ,  $P = 0.108$ ) 的相关性未达统计学显著性差异。ESR 与 CRP ( $r = 0.719$ ,  $P = 1 \times 10^{-6}$ ), RF ( $r = 0.397$ ,  $P = 7.99 \times 10^{-4}$ ) 和 DAS28 评

分( $r = 0.774, P = 1 \times 10^{-6}$ ) 均呈正相关 CRP 也与 DAS28 评分呈正相关( $r = 0.719, P = 1 \times 10^{-6}$ )。RF 和 CCP( $r = -0.344, P = 0.004$ ), DAS 28 评分( $r = -0.304, P = 0.012$ ), 腰 BMD 值( $r = -0.286, P = 0.018$ ), 腰 T 值( $r = -0.247, P = 0.042$ ) 均呈正相关。BAP 与骨折风险( $r = 0.314, P = 0.009$ ) 和髌骨折风险( $r = 0.345, P = 0.004$ ) 均呈正相关。 $\beta$ -crosslaps 和 Sharp 放射学评分呈正相关( $r = 0.776, P = 1 \times 10^{-6}$ ) (图 1)。腰 BMD, 腰 T 值, 髌 BMD, 髌 T 值, 骨折风险和髌骨折风险均两两存相关性( $P = 1 \times 10^{-6}$ )。

表 2 RA 患者的血清学标记、BMD 值和放射学评分

Table 2 Levels of biomarkers, bone mineral density, and radiographic score in RA patient

|                                                                  | RA 患者 (n=68)<br>RA cohort |
|------------------------------------------------------------------|---------------------------|
| 钙 (mmol/l)<br>Calcium (mmol/l)                                   | 2.26 $\pm$ 0.13           |
| 25 羟维生素 D3 (ng/ml)<br>25(OH) 2D3 (ng/ml)                         | 24.04 $\pm$ 11.54         |
| 骨性碱性磷酸酶 (U/L)<br>BAP (U/L)                                       | 13.92 $\pm$ 5.87          |
| $\beta$ 胶原特殊序列 (ug/l)<br>$\beta$ -crosslaps (ug/l)               | 452.87 $\pm$ 202.40       |
| 腰椎 BMD 值 (g/cm <sup>2</sup> )<br>Lumbar BMD (g/cm <sup>2</sup> ) | 0.75 $\pm$ 0.16           |
| 腰椎 T 值<br>Lumbar T score                                         | -2.67 $\pm$ 1.56          |
| 髌 BMD 值 (g/cm <sup>2</sup> )<br>Hip BMD (g/cm <sup>2</sup> )     | 0.59 $\pm$ 0.15           |
| 髌 T 值<br>Hip T score                                             | -2.45 $\pm$ 1.31          |
| 骨折风险 (%)<br>Fracture risk (%)                                    | 10.30 $\pm$ 9.19          |
| 髌骨折风险 (%)<br>Hip fracture risk (%)                               | 5.19 $\pm$ 7.59           |
| Sharp 总分<br>Total Sharp score                                    | 150.76 $\pm$ 59.71        |

### 3 讨论

对于绝经后 RA 而言,骨量减少是骨形成和骨吸收的失衡所致。另外,疾病的高度活动亦会诱发骨转换增加。BAP 是重要的骨形成标记,而  $\beta$ -crosslaps 则是骨吸收标记。短期的依那西普治疗后 BAP 水平升高,提示骨代谢平衡的重建<sup>[8]</sup>。已有研究表明, $\beta$ -crosslaps 水平在 RA 组患者表达升高,但差异没有显著性<sup>[9]</sup>。在英夫利昔单抗治疗后血清  $\beta$ -crosslaps 显著下调<sup>[10]</sup>,但与 ESR 和 CRP 不相关<sup>[11]</sup>。我们的研究表明,高水平的  $\beta$ -crosslaps 与

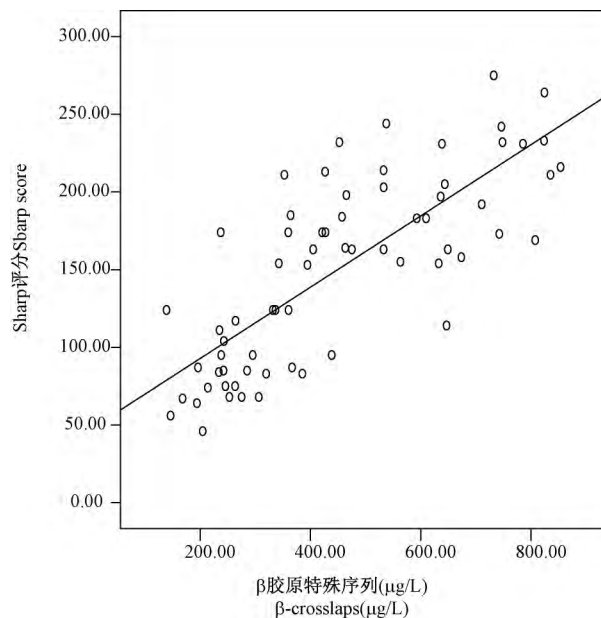


图 1 绝经后 RA 患者血清  $\beta$ -crosslaps 水平( $452.87 \pm 202.40$  ug/l) 与 Sharp 评分( $150.76 \pm 59.71$ ) 呈正相关( $r = 0.776, P = 1 \times 10^{-6}$ )

Fig. 1 Serum  $\beta$ -crosslaps level ( $452.87 \pm 202.40$  ug/l) was positively correlated with Sharp score ( $150.76 \pm 59.71$ ) in postmenopausal women with RA ( $r = 0.776, P = 1 \times 10^{-6}$ ).

RA 的放射学进展相关。 $\beta$ -crosslaps 可用于筛选出现高风险低 BMD 的群体。我们的研究也证实了骨吸收作用超过了骨形成从而导致疾病的发生进展。尽管积极抗炎治疗疾病仍显著进展的患者往往预后不佳。 $\beta$ -crosslaps 与疾病活动度无关而与 Sharp 评分相关,很可能对疾病进展预后判断有潜在价值。

RA 患者维生素 D 缺乏非常普遍,而且与高疾病活动度相关<sup>[12]</sup>。维生素 D 多态性与低维生素 D 水平和髌骨折的发生增加有关<sup>[13]</sup>。维生素 D 缺乏可能影响 Th17 应答和微血管功能从而参与发病<sup>[14]</sup>。但 RA 患者血清钙水平尚有争议<sup>[15,16]</sup>。在研究中我们未发现钙和维生素 D 之间存在相关性,可能的原因在于无法获得这些指标的日均摄入量从而作校正。接近 95% 的患者 BMD 值下降且超过半数有骨质疏松。随着年龄的增长,BMD 值和 T 值逐渐降低,与年龄和髌 BMD 值和 T 值呈负相关相一致。但腰椎 BMD 和 T 值与年龄不显著相关,可能因为伴随存在腰椎退行性骨关节炎。骨质疏松的治疗推荐从饮食和/或药物摄入足够的钙和维生素 D,这一措施是否能改善 RA 的骨质疏松有待进一步研究。

炎症和放射学进展是 RA 发病的两大重要元素。一些指标如 ESR, CRP 和 DAS28 反映疾病的炎症反应,而其他指标可能会参与疾病的进展。疾病缓慢进展的过程中骨形成和骨吸收并存。代表着骨吸收的标记  $\beta$ -crosslaps 在绝经后女性 RA 患者中可能预示着放射学进展。

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