SMGroup

SM Journal of Orthopedics

Research Article

The C-Terminal Telopeptide of Type I Collagen (CTX-I) Bone Resorption Marker in Osteoporotic Fractures: A Comparison of Hip and Radius Fractures in Spanish Adults. A Preliminary Study

Gutiérrez-Carbonell P[1]*, Ojeda-Peña M[1], Pelllicer-Garcia V[1], Moril-Peñalver L[1] and Gil-Orts R[2]

[1]*Service of Orthopaedic Surgery, General Hospital of Alcoy (Alicante), Spain*
[2]*Service of Laborary, General Hospital of Alcoy (Alicante), Spain*

Article Information

Received date: Oct 20, 2015
Accepted date: Nov 07, 2015
Published date: Nov 09, 2015

***Corresponding author**

Pedro Gutiérrez Carbonell, General Hospital of Alcoy (Alicante), Spain, Tel: 00 34 606 468 139; Fax: 00 34 965 24 59 71; Email: gutierrez_ped@gva.es

Abstract

Background: C-Terminal Telopeptide of type I collagen (CTX-I) is a bone marker of resorption. We study levels and compare levels in hip and wrist fractures.

Material and methods: Our study population included 82 men and postmenopausal women with hip fractures and 27 with radius fractures. CTX-I serum concentrations (measured in nanograms/milliliter) in the blood were measured using immunoassay. Levels above 0.60 ng/ml and 0.30 ng/ml were considered to be abnormal for women and men, respectively. Statistics: descriptive, t-test, and linear regression statistics were performed. The significance level was set at $p < 0.05$.

Results: The mean ages were 83.3 years and 74.1 years for patients with hip and radius fractures, respectively. The mean CTX-I serum concentrations were 0.74 ng/ml in patients with hip fractures and 0.64 ng/ml in patients with radius fractures. Above normal CTX-I concentrations were seen in 62% of the women with hip fractures and all of the men and 50% of all patients with radius fractures. Neither age nor sex influenced the CTX-I levels in patients with hip or wrist fractures. Trochanteric fractures had higher β-crosslaps than did cervical fractures. Serum CTX-I levels were significantly higher in hip fractures than in radius fractures independently of age ($p<0.001$).

Conclusion: Resorption bone markers are higher in patients with hip fractures than in patients with radius fractures. In our study, patients with trochanteric hip fractures had greater CTX-I levels than did patients with cervical fractures. All males and most women with fractures had high CTX-I levels, regardless of age.

Level of Evidence: Level 4.

Introduction

Osteoporosis is a silent disease with high medical, economic and social costs. Osteoporotic fractures are a particularly serious complication of the disease. Seventy percent of fractures in people over 45 years are due to osteoporosis [1]. Hip fractures are one of the most serious consequences of this disease, with high health and social costs. Only 50% of patients recover prior levels of functioning, and hip fractures are associated with a 12-35% mortality rate. Hip fractures account for 14% of all osteoporotic fractures, and the cost of hip fractures comprise about 60% of the total cost of care [1-3]. Wrist fractures comprise 19% of all fractures associated with osteoporosis, result in functional consequences in a third of patients, and represent 6% of the total treatment costs of all fractures. In fact, wrist fractures are considered to be a "sentinel fracture" of other osteoporotic fractures, preceding those fractures by several years [1-5].

Measures of blood and urine markers of bone resorption are correlated with the amount of degraded type I collagen (CTX-I) (β-Crosslaps), which constitutes 90% of bone proteins. This marker detects the β-isomer form of type I collagen carboxy-terminal telopeptide from bone in osteoporotic hip and wrist fractures. At present, measurement of these markers is considered to be a valid clinical method for determining the balance between bone formation and resorption, and for monitoring the response of patients to antiresorptive treatment [6-8].

Our aim was to study the serum CTX-I (β-Crosslaps) bone resorption marker in men older than 65 years and postmenopausal women from Spain for to know cut-off levels of CTX in this osteoporotic fractures and to define osteoporotic patients with higher risk of fracture and consecutively monitoring treatment of them.

Material and Methods

Our sample included 82 patients with hip fractures and 27 patients with distal radius fractures that occurred between 2010 and 2012. This study was approved by our Ethic Committee and has

Table 1: CTX-I serum levels in hip and distal radius fractures in total cases, gender and side.

	CTX-I levels in hip fractures (Mean ± SD*) (Range) (95% CI **)	CTX-I levels in distal radius fractures (Mean ± SD*) (Range) (95% CI **)
Total cases	0.74 ng/ml ± 0.39* (range: 0.2-2.68 ng/ml)	0.64 ng/ml ± 0.28* (range: 0.17-1.16 ng/ml)
Male	0.67 ng/ml ± 0.26* (** 0.52 -0.82)	0.64 ng/ml ± 0.22* (** 0.43-0.84)
Female	0.75 ng/ml ± 0.41 (** 0.65- 0.85)	0.64 ng/ml ± 0.29 (** 0.49-0.78)
Right-sided	0.78 ng/ml ± 0.44 (** -0.08-2.57)	0.59 ng/ml ± 0.28 (** 0.41-0.76)
Left-sided	0.69 ng/ml ± 0.31 (** -0.08-2.57)	0.75 ng/ml ± 0.23 (** 0.60-0.90)

*Standard Deviation
**95% Confidence Interval

therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all persons gave their informed consent prior to their inclusion in the study. The mean age for hip fractures was 83.3 years with a range of 65-94 years (SD: 5.7). Of these fractures, 58 (70.7%) were trochanteric fractures and 24 (29.3%) were cervical fractures. Of these subjects, 14 (17.1%) were men and 68 (82.9%) were women. The fractures were right-sided in 29 (35.5%) cases and left-sided in 53 (64.5%) cases. All wrist fractures were comminuted and involved the joint. The mean age of patients with a wrist fracture was 74.1 years, with a range of 54-90 years (SD: 8.6). Of these cases 7 (25.9%) were men and 20 (74.1%) were women. Right-sided fractures were seen in 12 (44.4%) cases, and left-sided fractures were seen in 14 (55.6%) cases. For each of the subjects a measurement of the serum concentration of the 8 amino acid β-isomer Crosslaps of the C-terminal portion of type I collagen or carboxy-terminal telopeptide (CTX-I) was obtained. The analytical test consists of an immunological test in vitro (electrochemiluminescence immunoassay) (Elecsys β-Crosslaps®, Roche Diagnostics, Manheim, Germany) to quantify the degradation. Results are given in nanograms/milliliter (ng/ml). According to the literature, and our laboratory, values above 0.6 ng/ml in postmenopausal women and above 0.3 ng/ml in men aged 50-70 years, are indicative of abnormal type I collagen degradation [1,6,9,10-12]. The completely automated test is performed in approximately 18 minutes and produces results using a calibration curve that is generated by the system from two points and a master curve provided in the reagent bar code. The measurement interval ranges from 0.01 to 6.0 ng/ml. Fasting blood samples were obtained between 7:30 and 9:30 in the morning, as there is less circadian rhythm variation in CTX- I degradation at that time [6-8,12-15]. Mean delay of surgery of hip fractures was 5 days and 3 days for wrist fractures; blood samples were obtained, at this hour, in morning of day prior to surgery. Patients were excluded if: a) previous antiresorptive treatment within 1 year prior to the fracture, b) being treated antiresorptive medications at the time of fracture, c) had primary or metastatic tumors in any location, d) had undergone bowel resections, had nephropathy with pathological levels of creatinine and creatinine clearance less than 60 ml/min, e) were on anticonvulsant treatment, f) Paget's disease, or g) rheumatoid or microcrystalline arthritis [8,12].

Table 2: CTX-Iserum levels in Trochanteric and Cervical hip fractures.

Types of Fractures	CTX-I levels (Range)(Mean ± SD*) (Range) (95% CI **)
Trochanteric fractures	0.78 ± 0.4* ng/ml (range: 0.31-2.68 ng/ml) (** 0.76-0.89)
Cervical fractures	0.62 ± 0.33* ng/ml (range: 0.19-1.69 ng/ml) (** 0.48-0.76)

*Standard Deviation
**95% Confidence Interval

Statistical analysis: Descriptive statistics, Kolmogorov-Smirnov test was applied to confirm a normal distribution. Parametric tests (Student's t-test), linear regression, and multiple linear regression were used to compare quantitative paired values and explore a possible relationship between age, sex, and CTX-I serum levels. A prior study of sample size was conducted using $\alpha = 0.05$ and $\beta = 0.10$ (type I and II errors). The level of statistical significance was set at $p < 0.05$.

Results

The calculated sample size required at least 13 subjects in each group. Descriptive statistics for each group are summarized in Tables 1 and 2. Of the patients with hip fractures, 38.3% had a CTX- I serum level below 0.60 ng/ml and 61.7% had levels above normal. In total, 63% of women and all men exceeded levels of 0.60 ng/ml and 0.30 ng/ml, respectively. Of the patients with radius fractures, 46.2% had a CTX-I level lower than 0.60 ng/ml and 53.8% had high levels. A total of 65.4% of women and all men exceeded the respective normal cut-offs. There was no difference in CTX-I levels between trochanteric and cervical fractures ($p = 0.06$), between men and women ($p = 0.36$), or between sides ($p = 0.39$) for both hip fracture ($p = 0.98$) and wrist fracture ($p = 0.13$). CTX-I levels were significantly higher in patients with hip fractures than in patients with wrist fractures ($p < 0.001$). Age did not influence CTX-I levels in patients with hip ($r = 0.18$, $p = 0.11$) or wrist ($r = 0.09$, $p = .64$) fractures. There was no difference in CTX-I levels according to age, sex, or fractures side.

Discussion

The relevance of bone fragility caused by osteoporosis is clearly evident. It has been estimated that the number of hip fractures will quadruple by 2020 and that approximately 20- 30% of patients with hip fractures will die within three months of the injury [1,2,16,17]. Radius fractures are the second most common fracture caused by bone fragility [18].

CTX-I is a measure of the β-isomer of type I collagen and is more specific for bone than for soft tissues. It seems that its levels are highest in the morning and lowest in the afternoon and at night, with variations of 5-10%. The most representative results are obtained between 7:30 and 9:30 in the morning. Therefore, we collected samples at this time to measure the maximum values of CTX-I [7-9,13,19,20]. We chose the Elecsys β-CrossLaps® method because of its sensitivity. This method's correlation with bone formation markers has been observed, allowing one to determine the degree of degradation of the C-terminal telopeptide of type I collagen (β-Crosslap) from bone, with intra- and interassay variability from 1.2-5%, respectively. This method can detect differences of 9-10% in the same individual with a sensitivity of 0.1 ng/ml, provided that the

immunoreactivity methodology, extraction time slot and fasting state of the patient are replicated [7-10,15,17,21,22]. Moreover, we elected to study the serum levels rather than the urine CTX-I levels, thus eliminating the confounding factor of impaired renal function and abnormal creatinine excretion. Abnormal creatinine values result in a 10-45% variability in CTX-I values [7,9,10,15,17,20]. Another factor that may distort the reliability of CTX-I is age. Age does not seem to significantly influence serum CTX-TELOC or Bone Mineral Density (BMD) in premenopausal women, but age has a significant influence on BMD in postmenopausal women [7,8,12,15,17,20]. In contrast, a significant negative correlation has been found between CTX-I levels and BMD at the distal radius in studies with 4 years of follow-up [17]. Additionally, large differences between sexes, races, and geographic areas have been described, suggesting that the risk factors for osteoporosis and fractures are multifactorial. The incidence of hip fractures is three times higher in females and up to seven times higher in some countries than in others. In general, the number of fractures is greater in northern Europe and lower in the Mediterranean region [23]. There are significant differences between people from different countries in terms of the levels of bone markers such as CTX-I. In fact, the levels of these markers are three to five times higher in the United States, Canada, and France than in Germany or the UK, and these levels are very low in Spain [12,22]. Toxins, such as tobacco, appear to affect levels of these markers. Female smokers have CTX-I levels that are 8% higher than non-smokers. On the contrary, these differences are not seen with alcohol consumption [12]. Other markers of bone resorption, such as pyridinoline and deoxypyridinoline exist but these markers they are not exclusively derived from bone, as is the case with CTX-I. Therefore, these markers have not been studied as extensively [10,13]. However, it has been shown that high CTX-I and deoxypyridinoline levels, combined with low BMD or even normal BMD, accurately predict risk for hip fracture. This risk doubles with a one standard deviation drop in BMD [12,13,20,24]. It has been reported that CTX-I has a sensitivity of 82% and a specificity of 100% in predicting increases in BMD after antiresorptive treatment and is more reliable than markers of bone formation [10,24]. Dual X-Ray Absorptiometry (DXA) and Quantitative Computed Tomography (QCT) are diagnostic methods that determine BMD and bone microarchitecture within an accuracy of 0.6-1.2%, allowing for prediction of risk of hip fracture with decreases in BMD [10,17,20]. However, these studies are costly, especially if used to track BMD and monitor the effect of different antiresorptive drugs [10-12]. In contrast, serum CTX-I is a valid clinical method for measuring the extent of bone resorption, ruling out metabolic pathologies, assessing risk for fractures and monitoring the effects of antiresorptive treatments in clinical practice. It has been reported that a 50% reduction in serum CTX-I would indicate that an antiresorptive therapy is effective in preventing fractures [8,12,17,23]. Moreover, a significant inverse correlation between BMD and serum CTX-I has been found. Thus, BMD increases of 3% at the lumbar spine are associated with 48% decreases in serum CTX-I after 6 months of estrogen therapy in postmenopausal osteoporotic women [8,10]. Moreover, the availability of CTX-I testing allows providers to test for compliance to antiresorptive treatments, detecting the almost immediate response of osteoformation markers to treatment with parathormones. Additionally, 2 to 3 months later there is a delayed response of bone resorption markers such as CTX-I with decreases in 54% of postmenopausal women treated with estrogens or parathyroid hormone [8,11,15,20,21,25]. Some authors advise combining CTX-I and bone densitometry, claiming that this method doubles the capacity to predict hip fracture in osteoporotic patients [7,15,17,21]. It has been found that 33 - 42% of postmenopausal women with osteoporosis exceeded the mean ± 2 SD of CTX-I levels, exhibiting elevated bone resorption and remodeling levels [12,15,17,20,26]. We have obtained CTX-I levels that exceed the normal value in 63% and 65% of women with hip and radius fractures, respectively, and in all men with fractures. That is, we found high CTX-I levels in a significantly higher percentage of people with hip or radius fracture, than in postmenopausal women without fracture. We have also found that all men with both types of fracture had higher than normal CTX-I levels. This finding is consistent with earlier studies of men with osteoporosis, but, again, it has not been reported in men with hip or radius fractures [15,27,28]. These findings are consistent with recent DXA and QCT studies that have found a lower BMD and trabecular thickness in a population of premenopausal women with hip and distal radius fractures [29]. Therefore, we believe that this preliminary study shows these original results. There are obvious limitations. A larger sample is needed to differentiate the importance of sex and to confirm whether there are statistically significant variations in CTX-I levels in different types of hip fracture. It is also clear that the use of a single bone marker for a problem as complex as osteoporosis is not reasonable. However, this reasonably economical and accurate clinical tool could, through periodic screening, identify population cut-offs for both sexes for risk of osteoporotic fractures. Finally, a larger sample size could help determine CTX-I cut- offs for Spanish adults with hip or distal radius fractures.

Ethical Approval

1. All patients gave the informed consent prior being included into the study;

2. All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments;

3. The study was approved by the Research Ethics Committee (or Institutional Review Board).

References

1. Bartl R, Frisch B. Osteoporosis. Diagnosis, Prevention, Therapy. Springer, Berlin. 2009.

2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007; 22: 465-475.

3. Cree MW, Juby AG, Carriere KC. Mortality and morbidity associated with osteoporosis drug treatment following hip fracture.Osteoporos Int. 2003; 14: 722-727.

4. Chapurlat RD, Bauer DC, Nevitt M, Stone K, Cummings SR. Incidence and risk factors for a second hip fracture in elderly women. The Study of Osteoporotic Fractures.Osteoporos Int. 2003; 14: 130-136.

5. Haentjens P, Autier P, Collins J, Velkeniers B, Vanderschueren D. Colles fracture, spine fracture, and subsequent risk of hip fracture in men and women. A meta-analysis. J Bone Joint Surg Am. 2003; 85-85A: 1936-1943.

6. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. J Bone Miner Res. 2000; 15: 1526-1536.

7. Looker AC, Bauer DC, Chesnut CH, Gundberg CM, Hochberg MC. Clinical use of biochemical markers of bone remodeling: current status and future directions.Osteoporos Int. 2000; 11: 467-480.

8. Fall P, Kennedy D, Smith J, Seobel M, Raisz G. Comparison of serum and urine assays for biochemical markers of bone resorption in postmenopausal women with and without hormone replacement therapy and in men. Osteoporos Int. 2000; 11: 481- 485.

9. Okabe R, Nakatsuka K, Inaba M, Miki T, Naka H. Clinical evaluation of the Elecsys beta-CrossLaps serum assay, a new assay for degradation products of type I collagen C-tlopeptides. Clin Chem. 2001; 47: 1410-1414.

10. Okabe R, Inaba M, Nakatsuka K, Miki T, Naka H, Moriguchi A, et al. Significance of serum CrossLaps as a predictor of changes in bone mineral density during estrogen replacement therapy; comparison with serum carboxyterminal telopeptide of type I collagen and urinary deoxypyridoline. J Bone Miner Metab. 2004; 22: 127-131.

11. Bauer DC1, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE. Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2006; 91: 1370-1375.

12. Glover S, Gall M, Schoenborn-Kellenberger O, Wagener M, Garnero P, Boonen S, et al. Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States. J Bone Miner Res. 2009; 24: 389-397.

13. Singer FR, Eyre DR. Using biochemical markers of bone turnover in clinical practice. Cleve Clin J Med. 2008; 75: 739-750.

14. Fall PM, Kennedy D, Smith JA, Seibel MJ, Raisz LG. Comparison of serum and urine assays for biochemical markers of bone resorption in postmenopausal women with and without hormone replacement therapy and in men. Osteoporos Int. 2000; 11: 481-485.

15. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. Committee of Scientific Advisors of the International Osteoporosis Foundation]. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000; 11: S2-17.

16. Myers AH, Robinson EG, Van Natta ML, Michelson JD, Collins K. Hip fractures among the elderly: factors associated with in-hospital mortality. Am J Epidemiol. 1991; 134: 1128-1137.

17. Wadddell J. Fractures of the proximal femur. Improving Outcomes. Elsevier-Saunders, Philadelphia. 2011.

18. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993; 137: 1001-1005.

19. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study.J Bone Miner Res. 1996; 11: 1531-1538.

20. Garnero P, Borel O, Delmas PD. Evaluation of a fully automated serum assay for C-terminal cross-linking telopeptide of type I collagen in osteoporosis.Clin Chem. 2001; 47: 694-702.

21. Licata AA. Biochemical markers of bone turnover: useful but underused. Cleve Clin J Med. 2008; 75: 751-752.

22. Cohen FJ, Eckert S, Mitlak BH. Geographic differences in bone turnover: data from a multinational study in healthy postmenopausal women. Calcif Tissue Int. 1998; 63: 277-282.

23. Johnell O, Gullberg B, Allander E, Kanis JA; MEDOS Study Group. The apparent incidence of hip fracture in Europe: a study of national register sources. Osteoporos Int. 1992; 2: 298-302.

24. Johnell O, Odén A, De Laet C, Garnero P, Delmas PD. Biochemical indices of bone turnover and the assessment of fracture probability. Osteoporos Int. 2002; 13: 523-526.

25. Quesada-Gómez JM, Muschitz C, Gómez-Reino J, Greisen H, Andersen HS. The effect of PTH (1-84) or strontium ranelate on bone formation markers in postmenopausal women with primary osteoporosis: results of a randomized, open-label clinical trial. Osteoporos Int. 2011; 22: 2529-2537.

26. Martínez J, Olmos JM, Hernández JL, Pinedo G, Llorca J. Bone turnover markers in Spanish postmenopausal women: the Camargo cohort study. Clin Chim Acta. 2009; 409: 70-74.

27. Szulc P1, Garnero P, Munoz F, Marchand F, Delmas PD. Cross-sectional evaluation of bone metabolism in men.J Bone Miner Res. 2001; 16: 1642-1650.

28. Fatayerji D, Eastell R. Age-related changes in bone turnover in men. J Bone Miner Res. 1999; 14: 1203-1210.

29. Rozental TD, Deschamps LN, Taylor A, Earp B, Zurakowski D. Premenopausal women with a distal radial fracture have deteriorated trabecular bone density and morphology compared with controls without a fracture. J Bone Joint Surg Am. 2013; 95: 633-642.