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ORIGINAL PAPER

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# Elevated levels of serum type I collagen C-telopeptide in patients with rapidly destructive osteoarthritis of the hip

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**Abstract** We compared type I collagen degradation using serum cross-linking C-terminal telopeptide (ICTP) in 18 patients with rapidly destructive osteoarthrosis and in 20 patients with slowly progressive osteoarthrosis of the hip. The diagnosis was established by clinical examination and radiographic evaluation. Total hip arthroplasty was performed in all patients. Serum levels of ICTP, bone-specific alkaline phosphatase, osteocalcin and N-terminal propeptide were studied. Patients with rapidly destructive osteoarthrosis had higher mean (SD) serum ICTP levels than patients with slowly progressive osteoarthrosis [13.2 (5.6) versus 3.7 ng/ml (1.4), $p$=0.001] whereas no significant difference of all other markers was seen between the groups. Elevation of ICTP levels correlated significantly with decreased joint-space width assessed by radiographs of the hip ($p$=0.01). Our data suggest that rapidly destructive hip osteoarthrosis is associated with elevated serum ICTP levels, reflecting increased collagen type I degradation.

**Résumé** Nous avons comparé la dégradation du collagène type I en utilisant le cross-linking du telopeptide Terminal C (ICTP) chez 18 malades avearthrose rapidement destructrice et chez 20 malades avecarthrose lentement progressive de la hanche. Le diagnostic a été établi par examen clinique et évaluation radiographique. L'arthroplastie totale de la hanche a été exécuté chez tous les malades. Le niveau sérique d'ICTP, des phosphatases alcalines osseuse spécifiques, de l'ostéocalcine, et du propeptide N-Terminal a été étudié. Les malades avec arthrose rapidement destructrice avaient une moyenne du niveau d'ICTP nettement plus haute que les malades avec arthrose lentement progressive [13.2 (5.6) vs 3.7 ng/ml (1.4), $p$=0.001], alors qu'aucune différence notable de tous les autres marqueurs n'a été notée entre les groupes. L'élévation de niveau de l› ICTP était en corrélation avec la hauteur de l'interligne articulaire apprécié par des radiographies ($p$=0.01). Nos données suggèrent que l'arthrose rapidement destructive est associé à une élévation sérique de l'ICTP reflétant une augmentation de la dégradation du collagène de type I.

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## Introduction

Rapidly destructive osteoarthritis (OA) of the hip is an uncommon subset of OA that affects mainly elderly women and leads to painful disability requiring total joint replacement [17, 19, 21]. Characteristically, the average duration of symptoms is significant shorter in patients with rapidly destructive OA, and joint-space narrowing has been shown to progress consistently faster, exceeding an annual rate of 2 mm in most patients [15]. On MRI, involvement of the femoral head and the acetabulum exhibiting a bone marrow edema-like pattern can be observed [2]. In advanced stages, destruction of subchondral bone with complete loss of joint space, fragmentation, and subluxation of the joint have been observed [7, 19]. Severe destruction of cartilage and bone along with invasion of nonspecific granulation tissue composed of macrophages and fibroblastic cells are consistent histological features, although a potential causative relationship between ischemic necrosis of the femoral head and rapidly destructive OA is still subjected to controversial debates [14, 22]. Initially, the disease affects articular cartilage in which the most abundant protein is collagen type II. Accordingly, urinary levels of type II collagen C-telopeptide (CTX-II) have been reported to be significantly higher in patients with rapidly destructive hip OA than in patients with slowly progressive hip OA [8]. Increased levels of matrix metalloproteinases (MMP-3 and -9) and decreased levels

of tissue inhibitor of matrix metalloproteinases (TIMP) in serum and joint fluid have pointed to a basic involvement of MMP in the pathogenesis of rapidly destructive hip OA [3, 12, 16]. Serum levels of C-terminal cross-linking telopeptide of collagen type I (ICTP) have been shown to reflect degradation of collagen type I in various bone pathologies, including rheumatoid arthritis [10], neuro-osteoarthropathy of the foot [18] and aseptic loosening after total hip arthroplasty (THA) [24]. Furthermore, measurement of collagen type I metabolites has been reported to enhance the diagnostic sensitivity even in patients with monostotic diseases such as Paget's disease [5]. Thus, evaluation of serum ICTP levels seems to be a promising approach for investigation of rapidly destructive OA. Consequently, this study aimed at comparing serum levels of ICTP in patients with rapidly destructive and slowly progressive OA of the hip.

## Patients and methods

This study was conducted in 38 patients [32 women, six men; mean (SD) age 69 (12.3), range 49–83 years] who underwent THA for treatment of primary hip OA. The diagnosis of rapidly destructive hip OA ($n$=18 patients) was based on radiographic examinations (at least two radiographs within 12 months before surgery), severe hip pain and disability, symptom onset within the past 2 years and absence of detectable inflammatory or crystal-induced joint disease [19]. Macroscopic findings during THA and examination of hip arthroplasty specimens (available in 12 patients) confirmed the diagnosis of rapidly destructive hip OA. Presence of slowly progressive hip OA was determined clinically and radiologically in the remaining 20 patients. Joint-space width (JSW) was documented on at least two pelvic radiographs obtained before surgery. Radiographic manifestations were evaluated as follows: subchondral sclerosis and cysts, osteophyte formation, minimal JSW, femoral-head flattening with or without eccentric depression, fragmentation and subluxation.

Exclusion criteria comprised the presence of infectious or inflammatory joint disease, impaired renal clearance, aseptic osteonecrosis, Paget's disease of the bone, and congenital hip dislocation. Medication affecting bone metabolism, such as bisphosphonates, calcium or vitamin D supplements or hormone replacement therapy was not present in any patient. Major bone surgery, such as total joint replacement, had not been performed in any patient 24 months prior to THA [23]. In patients with rapidly destructive hip OA, the presence of atherosclerotic disease and a history of minor trauma was recorded in one patient each whereas two patients with atherosclerotic disease and no patient with a history of trauma were identified in patients with slowly progressive hip OA. Clinical examination was performed using the Harris hip score (HHS, 100 points = normal hip) and a full clinical history was obtained at entry [11]. Furthermore, data on patients' weight, height, symptom duration and body mass index (BMI) were obtained. Involvement of the contralateral hip was seen in four patients with rapidly destructive versus six patients with slowly progressive hip OA; however, none of the patients had been treated with THA.

Molecular markers of bone metabolism were measured in the peripheral blood of all patients. Samples were obtained between 8 and 10 A.M. on the day of surgery after overnight fasting to minimize possible influences of circadian variations [20]. Levels of osteocalcin (OC) and bone-specific alkaline phosphatase (bone ALP) were evaluated using ELSA-Osteo (CIS Bio Int, Gif-sur-Yvette, France) and Tandem-ostase (Hybritech, San Diego, CA, USA), respectively. Concentrations of ICTP and N-terminal propeptide of procollagen type I (PINP) were assessed using radioimmunoassays supplied by Orion Diagnostica (FIN-02101 Espoo, Finland). Statistical analysis was performed using "Statview" statistical software (SAS, Adept Science Institute, Letchworth, UK). Because the distribution of biochemical markers was not normal in all patients, levels were logarithmically transformed before analyses. Student's $t$ test was used to determine the significance of continuous data and linear regression analysis was used to determine the relationship between two different variables. Statistical significance was set at $p<0.05$. Written informed consent was obtained from all patients.

**Table 1** Characteristics of patients with rapidly destructive and slowly progressive hip osteoarthritis (OA). *ICTP* serum cross-linking C-terminal telopeptide, *PINP* N-terminal propeptide of procollagen type I, *OC* osteocalcin, *CRP* C-reactive protein

| Parameters | Rapidly destructive ($n$=18) | Slowly progressive ($n$=20) | Rapidly versus slowly progressive ($p$ value) |
|---|---|---|---|
| Gender (f/m) | 16/2 | 16/4 | 0.63 |
| Age (years) | 72.8±9.6 | 62.8±11.1 | 0.02 |
| Weight (kg) | 75.6±8.1 | 79.1±13.3 | 0.42 |
| Height (cm) | 169.1±6.5 | 170.8±9.8 | 0.57 |
| Body mass index (kg/m$^2$) | 26.5±3.5 | 27.1±3.3 | 0.71 |
| Minimal joint-space width (mm) | 0.55±0.39 | 1.82±0.88 | 0.001 |
| Serum ICTP (ng/ml) | 13.2±5.6 | 3.7±1.4 | 0.002 |
| Serum PINP (ng/ml) | 50.4±24.9 | 39.3±12.8 | 0.16 |
| Serum OC (ng/ml) | 12.1±4.9 | 13.4±9.2 | 0.61 |
| Serum bone ALP (ng/ml) | 13.7±9.8 | 12.9±12.2 | 0.92 |
| Serum CRP (ng/ml) | 14.3±9.6 | 6.8±6.1 | 0.01 |

## Results

The average duration of symptoms was 10.1±5.3 months in patients with rapidly destructive hip OA whereas patients with slowly progressive hip OA had been symptomatic for at mean 30.1±12.3 months ($p<0.001$). As shown in Table 1, patients with rapidly destructive hip OA were older than patients with slowly progressive OA; however, comparison of height, weight and BMI did not produce a statistical significance. HHS, obtained before surgery, were significantly higher in patients with slowly progressive hip OA (37.6±8.7 points) than in patients with rapidly destructive disease (24.1±11.1 points, $p=0.001$). Joint-space narrowing was more severe in patients with rapidly progressive hip OA ($p=0.001$) whereas presence of osteophytes was more frequent in patients with slowly progressive hip OA (11 patients versus four patients with a rapid progression of the disease). Femoral-head flattening was seen in 15 patients with rapidly destructive hip OA, of whom eight had an eccentric depression at the lateral femoral surface molding into the adjacent acetabulum (Fig. 1). Subluxation of the hip joint was seen in four patients with rapidly destructive hip OA but was not present in patients with slowly progressive hip OA.

Patients with rapidly destructive hip OA had higher ICTP levels ($p=0.001$) than those with slowly progressive disease whereas no significant difference was observed for all other markers tested (Fig. 2). When comparing serum levels of biochemical markers with joint-space narrowing in all patients with hip OA, a significant correlation was found only for ICTP ($r=-0.49$, $p=0.01$). Correlation of age and marker levels, again, only produced a clear significance for ICTP ($r=0.47$, $p=0.01$). After adjustment for age, patients with rapidly destructive hip OA still had higher ICTP levels than patients with a slow progression of the disease ($p=0.01$). In the whole group of patients with hip OA, levels of OC and PINP were found to correlate with each other ($r=0.39$, $p=0.03$) but not with levels of ICTP ($p=0.53$ and $p=0.29$, respectively). Among patients with rapidly destructive hip OA, 17 of 18 had increased serum ICTP levels (normal range 1.3–5.6 ng/ml) whereas only 3/20 with slowly progressive hip OA had elevated ICTP levels. Levels of OC and bone ALP were increased above normal limits in three and two patients with slowly progressive hip OA, respectively, whereas serum bone ALP was increased in three patients with rapidly destructive hip OA. Finally, serum concentrations of PINP and OC were not elevated in any patient with hip OA. Serum ICTP levels of patients with slowly progressive hip OA (at mean 3.7±1.4 ng/ml) were not different from healthy controls (at mean 3.9±1.6 ng/ml) of a previous study [1].

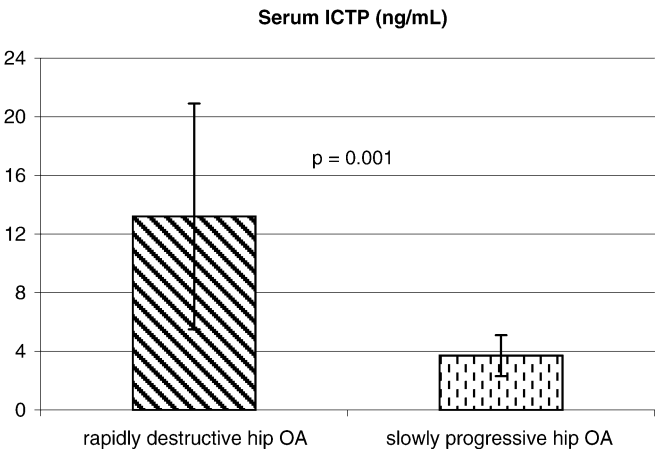


**Fig. 2** Serum cross-linking C-terminal telopeptide (ICTP) levels ± SD in patients with rapidly destructive and slowly progressive hip osteoarthritis (OA).

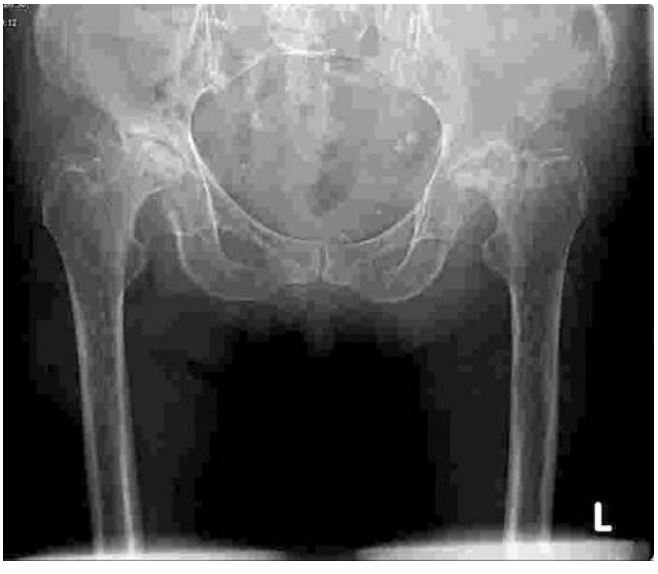


**Fig. 1** Anteroposterior radiograph obtained in a 72-year-old woman with rapidly destructive osteoarthritis (OA) of both hip joints. Severe flattening of both femoral heads associated with superolateral subluxation, sclerosis, and subchondral defects is seen.

## Discussion

Despite numerous attempts to elucidate pathogenetic factors, the origin and the complex nature of rapidly destructive hip OA still remain unclear [3, 7]. Radiographic findings in this disease can mimic those of other disorders, such as septic arthritis, rheumatoid and seronegative arthritis and primary osteonecrosis with secondary OA [21]. However, none of our patients had clinical, pathologic or laboratory evidence of these entities. Repeated minor trauma with subsequent stress fractures, excessive locomotor activity and femoral-head hypoxia due to atherosclerotic vasculopathy have been proposed as predisposing factors [21]. Yet these factors were only present in two of our patients with a rapid progression of the disease, rendering a causative explanation unlikely. Clinical examination showed significantly decreased HHS in our patients reflecting severe pain and disability in rapidly destructive hip disease [7, 21].

Previous studies on disease activity and collagen type I degradation in patients with neuro-osteoarthropathy of the foot [18] and reactive arthritis have shown a clear cor-

relation between elevation of serum ICTP levels and extent and activity of joint disease [6, 13]. However, serum levels of ICTP in patients with rapidly destructive hip OA have not been reported so far. When looking at prognostic molecular markers in patients with hip OA, Conrozier et al. [4] found a nearly threefold increase of CRP, reflecting a certain degree of inflammation in these patients. Our results of a twofold increase of CRP in serum of patients with rapidly destructive hip OA when compared to patients with slowly progressive disease are consistent with previous findings and underline the existence of inflammatory processes in the course of this disease. Furthermore, increased levels of MMP-2, -3 and -9 in serum and joint fluid and decreased serum levels of TIMP have been demonstrated in patients with rapidly destructive hip OA [12, 16]. Interestingly, MMP-2, -9, and -14 have been shown to release ICTP but not CTX-I from bone collagen, indicating two different collagenolytic pathways for these type I collagen fragments [9]. Measurement of urinary CTX-II, a specific marker for cartilage degradation, has shown higher urinary levels in patients with rapidly destructive hip OA when compared with patients with slowly progressing OA [8]. Yet, levels of urinary free deoxypyridinoline (free DPD), a marker of bone resorption, were not elevated in patients with rapidly destructive hip OA. It was hypothesized that levels of this bone resorption marker mainly reflect the overall skeletal change of bone, which can be altered by various factors besides abnormalities of subchondral bone [8]. Unlike the findings of Garnero et al. of unaltered free DPD levels [8], we were able to detect elevated levels of ICTP, reflecting bone resorption in our patients with rapidly destructive hip OA. Apart from decreased minimal JSW, the extent of bone loss observed on preoperative radiographs—femoral-head flattening was seen in 15 patients with rapidly destructive hip OA of whom eight patients had an eccentric depression at the lateral femoral surface molding into the adjacent acetabulum—seems to indicate that serum ICTP levels in our patients originate from focal degradation of collagen type I at the affected hip joint rather than from other skeletal sources. Clinically, none of our patients had symptomatic OA of the knees, spine, or hands, although we did not perform radiographs of these joints. Thus, we could not investigate the potential contribution of these other joints to serum levels of these markers in our patients. However, the poor quality of bone observed during surgery and, more importantly, the threefold increase in mean ICTP levels in our patients with rapidly destructive hip OA, strongly indicate the existence of a causal relation. A further limitation of our study is the lack of healthy controls, which could have been used to establish a cutoff point of serum ICTP levels. However, serum ICTP levels in patients with slowly progressive hip OA were not different from serum ICTP concentrations in healthy patients from a previous study [1]. Furthermore, owing to the singular assessment at the time of surgery, no statement regarding baseline levels and a possible temporary change in the course of the disease can be made.

In conclusion, determination of ICTP in serum may be useful for identification and monitoring of patients with rapidly destructive hip OA. Further work is needed to confirm these data in larger longitudinal studies.

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