Epidemiological, clinical, biological and radiological differences between atrophic and hypertrophic patterns of hip osteoarthritis. A case-control study

Th. Conrozier[1], F. Merle-Vincent[4], P. Mathieu[1], M. Richard[2], H. Favret[1], M. Piperno[1], J. Caton[3], E. Vignon[1]

[1]Department of Rheumatology, Centre Hospitalier Lyon-Sud, Pierre-Bénite;
[2]Department of Biochemistry, Hopital Edouard Herriot, Lyon;
[3]Department of Orthopedics, Clinique Emilie de Vialar, Lyon, France.

Abstract

Objective

Lack of osteophytes (atrophic form) has been shown to be a factor in the severity of hip osteoarthritis (OA). The aim of this study was to determine the epidemiological, radiological and biological differences between the hypertrophic and atrophic forms of hip osteoarthritis.

Methods

25 patients with symptomatic hip OA (ACR criteria) and classified as having an atrophic form of OA based on the lack of osteophytes on standard radiograph of the pelvis, were matched for joint space width with 25 subjects with evidence of the hypertrophic form of hip OA. OA radiological severity was assessed using a scoring system and by computer measurement of the joint space width. Angles of hip dysplasia were measured. Serum hyaluronic acid, cartilage oligomeric matrix protein, collagenase, Type I procollagen, C-terminal crosslinking telopeptide of type I collagen and tissue inhibitor of métalloproteases-1 were assayed by immunoassay and C-reactive protein by ultrasensitive immunonephelemetry. Statistical analysis was performed using logistic regression, taking into account age, sex, body mass index, and bilaterality.

Results

Compared to hypertrophic OA, atrophic OA affected chiefly elderly women and was characterized by a smaller centre-edge angle and diffuse superior femoral head migration. It was less frequently bilateral. No statistically significant difference was found in the biological data between the two groups.

Conclusion

An atrophic bone response in hip OA occurs chiefly in women and is associated with poor coverage of the femoral head. Serum biomarkers able to demonstrate differences between the atrophic and hypertrophic patterns of OA are lacking.

Key words

Hip, osteoarthritis, biological markers, radiography, joint space measurement.

Please address correspondence and reprint requests to: Thierry Conrozier, MD, Service de rhumatologie, Centre hospitalier Lyon-Sud, 165 chemin du Grand-Revoyet, 69495 Pierre-Bénite cedex, France.
E-mail: thierry.conrozier@chu-lyon.fr

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Introduction

Osteoarthritis (OA) of the hip is one of the most common causes of pain and disability in adults aged 55 years and older (1) The age and sex standardized-incidence rate for the disease has been estimated to be between 47.3 and 88/100,000 person-years (2, 3), increasing with age to reach 445/100,000 in women aged 70-79 (3). A number of studies clearly suggest that the rate of progression of hip OA is very heterogenous among patients (4-7). Solomon *et al*. (8) suggested that the behaviour of coxarthrosis may be determined by three interacting factors such as cartilage degeneration, excessive mechanical stress, and the reparative bone response. When anatomical abnormalities and mechanical features are dominant, cartilage loss is localised, remodelling is good and the hip can stabilise. When inflammatory and degenerative features predominate, reparative new bone formation is minimal and progression is more rapid. The pattern of bone response to cartilage loss can be classified as hypertrophic or atrophic based on the presence or absence of osteophytes, respectively (Fig. 1).

There is strong evidence that lack of osteophytes (the atrophic form of OA) is associated with the faster progression of joint space narrowing and is a factor in the severity of hip osteoarthritis (6-10). The aim of the present study was to determine the epidemiological, clinical, radiological and biological differences between the atrophic and hypertrophic patterns of hip OA in order to propose hypotheses regarding the physiopathology of the disease.

Patients and methods

Patients and clinical data

This cross-sectional case-control study was conducted on 50 patients. Among 174 patients referred to our Department of Rheumatology for symptomatic hip OA, diagnosed according to the ACR criteria, 25 subjects (14.3%) had evidence of the atrophic form of hip OA. They were matched for hip joint space width (see below) with 25 of the 92 patients being followed in the same department who exhibited the hypertrophic pattern of the disease. All patients underwent standard antero-posterior X-ray of the pelvis and "faux-profil" (11) of the hips. Patients with hip OA secondary to alternative arthropathies were excluded (i.e. infectious or inflammatory arthritis, Paget's disease, aseptic osteonecrosis, or major congenital abnormalities such as congenital dislocation of the hip). All patients underwent a full clinical history and examination to obtain the following information: height, weight, body mass index (BMI), disease duration and date of diagnosis, history of hip joint trauma, risk of hip joint overwork (classified as low, normal or high) with regard to professional or sport activities (i..e. regular heavy lifting or strenuous walking and running), polyarticular OA involvement (Heberden or Bouchard's nodes; radiological spine OA or knee OA if x-rays available), and smoking status. Pain was self-assessed by the patients on a 100 mm visual analog scale (VAS) and disability relative to hip OAwas evaluated using the Lequesne algofunctional index (12) None of the patients presented clinically detectable disease that could interfere with the current dosage of the serum or urinary markers for OA. For each patient, all clinical and laboratory data were obtained on the day of the hip radiograph.

Radiographic data

All patients had radiographs of the pelvis taken using a standardized radiological procedure. Antero-posterior radiographs of the pelvis were taken with the patient in standing position with 20° of internal rotation of the lower limbs. The focus-film distance was 100 cm and the beam was aligned to the top of pubic symphysis. Lequesne "faux-profil" of the two hips was performed using the standardised published procedure (11).

Morphological evaluation

Osteoarthritis radiographic changes were graded according the modified Altman score (13) using a 5-point scale (0 to 4) for joint space narrowing (JSN), a 4-point scale (0 to 3) for osteophytes, a 3-point scale (0-2) for cysts and a 2-point scale (0-1) for sclerosis (13). The inter-observer kappa value

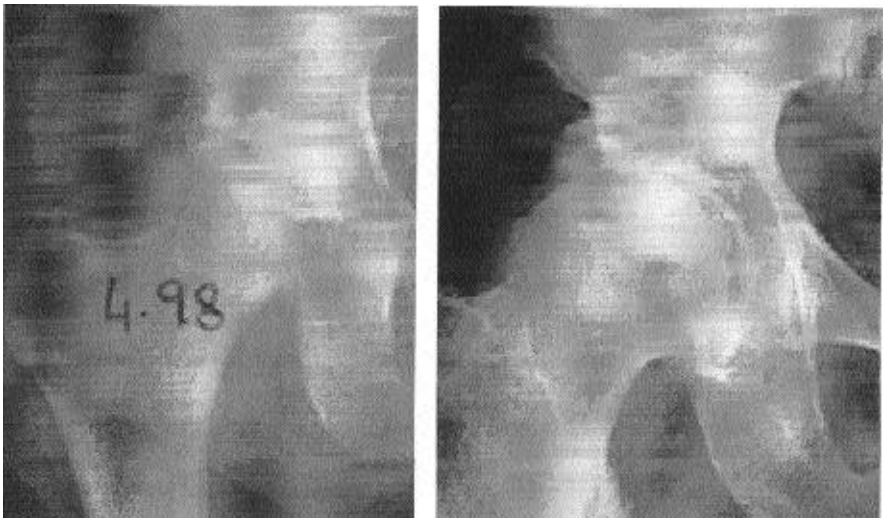

Fig. 1. Atrophic (**a**) and hypertrophic (**b**) patterns of hip osteoarthritis.

(95%CI) was 0.91 (0.88 – 0.94), 0.79 (0.71 – 0.87), 0.77 (0.67 – 0.87) and 0.76 (0.68 – 0.85) for each item, respectively.

Each hip was classified as hypertrophic or atrophic according to presence or lack of osteophytes. Osteophytes were assessed on both femoral head and acetabulum. Osteophyte grade was given by the highest grade. To be classified as atrophic, the hip had to be of grade 0 for osteophyte and >1 (definite) for JSN. To be classified as hypertrophic it must be of grade >1 (definite) for osteophyte whatever the JSN was. The intra-class coefficient of correlation (CI 95%) between repeated evaluation was 0.96 (0.91 – 0.99).

The pattern of femoral head migration within the acetabulum was classified as supero-lateral, supero- intermediate, supero-medial as proposed by Ledingham *et al*. (9).

Joint space measurement

The hip joint space width was determined based on a previously published method (14,15), with the help of a digitized image analysis computer using a specific software (Holy'S Actibase®, Lyon, France). The joint space contours were delineated with the mouse on the following margins: the superior convex edge of the femoral head and the inferior margin of the acetabulum. The joint space width at the narrowest point (minimal JSW) and the mean JSW were automatically calculated by the computer within this area. The intra-class coefficient of correlation between repeated measurements of a single film was 0.99. The standard deviation (SD) for repeated measurements of the same film was 0.15 mm so that the smallest detectable difference to be significant between two measurements was 0.3 mm (2SD). Patterns of hip joint dysplasia: head-neck-shaft angle (HNS), acetabular depth (AD) and centre-edge (CE) angle were also obtained using the computer (6).

Each patient with atrophic OA was matched by drawing lots for another patient with evidence of the hypertrophic form of OA and the same (± 0.30 mm) min JSW.

Biological data

Blood samples were obtained from each subject on the same day that the radiograph was taken. The serum was immediately frozen and stored at -25°C.

Inflammation markers

C reactive protein was assayed by ultra-sensitive immunonephelemetry (N Latex CRP mono™Behringwerke AG). The intra-assay coefficient of variation (CV) was 4.75% (16) and the threshold of detection was 0.175 mg/l.

Cartilage and synovium markers

Serum collagenolytic activity (MMP-1) was measured based on the digestion of fluorogenic peptide (DNP-Pro-Leu-Ala-Leu-Trp-Ala-ArgOH (17). The intra-assay coefficient of variation (CV) was 5-9%.

Tissue inhibitor of metalloprotease-1 (TIMP-1) was assayed using an ELISA technique (Biotrack TIMP-1™, Pharmacia Biotech). The intra-assay CV ranged from 8.9 and 11.4% (18).

The hyaluronic acid (HA) assay was performed using the Pharmacia HA test™ (intra-assay CV 6.4–7.2%) (19).

Cartilage oligomeric matrix protein (COMP) was analyzed by a newly developed sandwich ELISA method (Covalab, France). The intra-assay coefficient of variation (CV) was 8–20%.

Bone turnover markers

Type I procollagen was measured by a sandwich immunoassay (Prolagen-C™ Metra Biosystems) (CVs 55-6.8%) (21).

Serum β isomerised C-terminal cross-linking telopeptide of type I collagen (S-CTX-I) was measured by an immunoassay (Serum Crosslaps One Step ELISA™,Osteometer Biotech, Herlev Denmark) (CVs 4.7–4.9%) (22).

Statistical analysis

We chose to match "patients" (atrophic) and "controls" (hypertrophic) for joint space width but not for age and sex to eliminate the impact of disease severity, in particular for the biological data. Nevertheless, in the multivariate

Table I. Modified Altman score for osteoarthritis radiological assessment.

Joint space narrowing
- 0: no narrowing
- 1: mild or doubtful narrowing (< 33%)
- 2: moderate narrowing (34 – 66%)
- 3: severe narrowing (> 66% but no complete narrowing)
- 4: complete narrowing (100%)

Osteophytes (acetabulum and/or femoral head):
- 0: no osteophyte
- 1: mild or doubtful osteophyte
- 2: moderate osteophyte
- 3: large osteophyte

Sclerosis
- 0: no or doubtful sclerosis
- 1: evidence of sclerosis

Subchondral bone cysts
- 0: no or doubtful cyst
- 1: definite cyst
- 3: large cyst

analysis of biological data we systematically included age, gender bilaterality and BMI as possible confounding variables.

Statistical analysis was performed using the following procedures: patients with atrophic and hypertrophic OA were compared for each variable using the chi-square test and Wilcoxon rank test as appropriate, and then applying logistic regression including each variable that was found to be significant in the univariate analysis. Correlations between variables were investigated using Spearman's test. P values < 0.05 were considered statistically significant.

Table II. Epidemiological, clinical and radiological characteristics of patients suffering from atrophic hip osteoarthritis, matched by hip joint space width with patients suffering from hypertrophic hip osteoarthritis.

Variables	Hypertrophic OA		Atrophic OA		p
Sex: male/female	12/13	4/21	0.02		
Bilateral: yes/no	17/8	9/16	0.03		
Age (SD)	62.4	(1.8)	67.0	(2.0)	0.01
Pain on VAS mm (SD)	54.5	(25.5)	63.1	(6.9)	ns
Lequesne index (SD)	8.5	(0.9)	10.5	(0.8)	0.05
Disease duration [months] (SD)	67	(56)	14	(14)	0.0001
Months between onset and diagnosis (SD)	12	(11)	6	(4)	0.02
NSAIDs consumption (no. of pts.)	18	20	ns		
SMOADs consumption (no. of pts.)	13	13	ns		
Min JSWmm (SD)	1.8	(0.2)	1.6	(0.2)	ns
Mean JSWmm (SD)	2.4	(1.1)	2.3	(1.0)	ns
Centre edge angle° (SD)	31.9	(1.4)	26.6	(1.2)	0.004
Head neck shaft angle° (SD)	121.3	(7.5)	128.7	(1.2)	0.02
Acetabular depth (SD)	9.8	(1)	10.6	(0.9)	ns
Femoral head migration: SL/SI/SM/A	13/4/6/2		8/17/0/0		0.003

SD: standard deviation; JSW: joint space width; NSAIDs: non-steroidal anti-inflammatory drugs; SMOADs: structure-modifying drugs for osteoarthritis; SL: supero-lateral; SI: supero-intermediate.

Results

The characteristics of patients are summarized in Table II.

Epidemiological data

The atrophic form affected chiefly women (p = 0.02), at a more advanced age (mean difference 5 years, p= 0.01), and was responsible for more disability (Lequesne's index 10.5 versus 8.5, p = 0.05) than hypertrophic OA. Disease duration since the date of diagnosis was longer in patients with hypertrophic OA (67 versus 14 months; p < 0.0001) suggesting that joint space narrowing progression was slower. The time between the onset of symptoms and the diagnosis of hip OA was 6 and 12 months respectively in atrophic and hypertrophic OA (p = 0.02), showing that patients with atrophic OA needed to consult a physician earlier than patients with hypertrophic OA. Among the 25 patients with atrophic OA, 9 had a history of hip trauma versus only one of the subjects with hypertrophic OA(p = 0.005).

After adjustment for gender, there was no difference between the 2 groups regarding height, BMI, risk of hip joint overwork, polyarticular OA, smoking status and pain on the VAS.

Radiological data

In atrophic OA, the pattern of femoral head migration was more likely to be supero-intermediate (17/25), while supero-lateral migration was more frequent in the hypertrophic forms (13/25) (p = 0.003). Atrophic OA was also found to be less frequently bilateral (8/25 versus 16/25) (p = 0.03). Significant differences were also found between atrophic and hypertrophic OAfor the CE (p = 0.004) and HNS angles (p = 0.02) but not for AD.

Biological data

On univariate analysis no significant difference was found between the two groups for the biological markers. CRP (4.4 versus 3.5 mg/l), COMP (570.4 versus 383.7 ng/ml) and HA (133.8 versus 91.9 ng/ml) were slightly higher in atrophic than in hypertrophic OA (respectively +25%, +48.6% and +51%), but the differences were not statistically significant. HA and COMP concentrations were highly correlated (Rho 0.62, p = 0.005), while no other correlation was found between biological markers.

After adjustment for age, gender and BMI, logistic regression showed that atrophic OA was characterized by a shorter disease duration (p=0.03), a smaller centre-edge angle (p = 0.01), and was less frequently bilateral (p = 0.04) and more often of a supero-intermediate JSN topography (p = 0.02). No statistically significant difference was found for CRP, COMP, HA, TIMP-1, collagen C-terminal propeptide and S-

Table III. Biological characteristics of patients suffering from atrophic hip osteoarthritis, matched by hip joint space width with hypertrophic hip osteoarthritis patients (SD given between parentheses).

Markers	Hypertrophic OA		Atrophic OA		P
CRP(mg/l)	3.5	(0.6)	4.4	(0.8)	ns
COMP(ng/ml)	383.7	(37.9)	570.4	(86.6)	ns
TIMP-1 (ng/ml)	700.6	(46.5)	745.3	(27.6)	ns
HA(ng/ml)	91.9	(13.4)	133.8	(18.5)	ns
CP-I (ng/ml)	69.1	(24.5)	74.5	(31.8)	ns
S-CTX-I (pmol/l)	2778	(2200)	2817	(1764)	ns
MMP-1 (ng/ml)	405	(102.2)	389	(85.1)	ns

SD: standard deviation; CRP: C-reactive protein; COMP: cartilage ologomeric matrix protein, TIMP-1: tissue inhibitor of metalloprotease 1; HA: hyaluronic acid; CP-I: type I procollagen; S-CTX-I: serum β isomerised C-terminal cross linking telopeptide of type I collagen, MMP-1: metalloprotease 1.

CTX-1, HSN angle, AD, smoking cigarettes, generalized OA and history of hip overuse.

Discussion

The present results, despite the fact that they were obtained from a limited number of patients, demonstrated that age and gender were the major determinants of the atrophic pattern of osteoarthritis of the hip. These data are consistent with those of Ledingham *et al.* (9). These authors studied 211 patients with osteoarthritis of the hip and showed that gender was the main determinant of the pattern of osteoarthritis of the hip and that the atrophic form of OA was associated with more severe disease. They found that only 40% of the hips could be categorised as hypertrophic or atrophic. Using our radiological criteria 67.2% of the hips could be clearly classified as hypertrophic (52.9%) or atrophic (14.3%). In the other cases JSN and/or osteophyte were doubtful (grade I) and hips could not be strictly classified as hypertrophic or atrophic.

Although the present study was a cross-sectional one, the results suggest that atrophic OA leads to more severe and premature pain and disability than hypertrophic OA. Two longitudinal studies (6, 24) had previously demonstrated that the lack of osteophytes was associated with rapid progression of joint space narrowing. In a 7-year longitudinal trial of 61 patients who underwent total hip arthroplasty for hip OA (6), we showed that the atrophic form of OA was significantly different from hypertrophic OA in terms of the rate of joint space narrowing (0.74 vs 0.27 mm/year, $p < 0.001$), the time between diagnosis and THA(45.8 vs 98.9 months, $p < 0.002$) and the center-edge angle (28° vs 35, $p < 0.001$). Furthermore, most of the rapidly destructive forms of hip OA are of the atrophic form (25), suggesting that osteophytes could constitute a protective process against cartilage breakdown.

Osteoarthritis is defined as a focal lesion of articular cartilage, combined with a hypertrophic reaction in the subchondral bone and a new bone reaction at the margin joint. The mechanism of osteophytosis is probably an adaptive reaction of the joint to joint instability, or might be related to on-going repair reactions in the cartilage and or ligamentous structures of the damaged joint (23). In our study, patients with atrophic OA were mainly elderly women with superointermediate or superolateral joint space narrowing. No atrophic form was found in patients with superomedial or axial femoral head migration. One could speculate there is a lack of reparative processes in a particular subset of elderly women, particularly those with poor coverage of the femoral head, sometimes after hip trauma, but the reasons for this lack of a bone hypertrophic response remain unclear.

The present study was not able to demonstrate any biological difference between hypertrophic and atrophic OA. There are only a limited number of studies on the biological markers of hip OA (13, 16, 26-28). Serum C-reactive protein (CRP), measured by highly sensitive nephelemetry, was also reported to be increased in rapidly destructive hip OA (16) and was shown to be predictive of disease progression in knee OA (29). In the present study we did not find a clear relationship between the patterns of bone response and CRP levels since the results suggest that the increase in CRP serum levels in patients with atrophic OA was likely due in part to the older age of this subgroup. Several explanations may account for our somewhat disappointing results. Firstly, locally increased production of a marker in a single OA joint may induce only small variations in its serum concentrations, that remain below the limits of detection. Secondly, none of the putative markers being specific to joint tissues, production from other tissues may contribute to influence its serum level and thereby unmask mild variations originating from a damaged joint. Finally, the limited number of patients could also explain the insufficient statistical power of this study.

Although in our study none of the surrogate biological markers was discriminative between the atrophic and hypertrophic forms of OA, further studies will be necessary to assess the involvement of growth factors, i.e. local or systemic deficiencies in TGF beta (30), or in the pattern of the bone response to mechanical stress in hip OA.

References

1. FELSON DT: Epidemiology of knee and hip osteoarthritis. *Epidemiol Rev* 1988; 10: 1-18.
2. OLIVERIASA, FELSON DT, REED JI, CIRILLO PA, WALKER AM: Incidence of symptomatic hand, hip and knee osteoarthritis among patients in health maintenance organization. *Arthritis Rheum* 1995; 38: 1134-41.
3. WILSON MG, MICHET CJ, ILSTRUP DM, MELTON LJ: Idiopathic symptomatic osteoarthritis of the hip and knee. A population-based incidence study. *Mayo Clin Proc* 1990; 65: 1214-21.
4. HOAGLUND F, OISHI C, GIALAMAS G: Extreme variations in racial rates of total hip arthroplasty for primary coxarthrosis: a population-based study in San Francisco. *Ann Rheum Dis* 1995; 54: 107-10.
5. LEQUESNE M: La chondrométrie. Evaluation quantitative de l'épaisseur de l'interligne et de sa dégradation annuelle dans la coxarthrose. *Rev Rhum* [Ed. Fr.] 1995; 62: 165-8.
6. CONROZIER T, JOUSSEAUME CA, MATHIEU P *et al*.: Quantitative measurement of joint space narrowing progression in hip osteoarthritis: a longitudinal retrospective study of patients treated by total hip arthroplasty. *Br J Rheumatol* 1998; 37: 961-8.
7. DOUGADOS M, NGUYEN M, BERDAH L, MAZIÈRES B, VIGNON E, LEQUESNE M: Evaluation of the structure-modifying effects of diacerhein in hip osteoarthritis: ECHODIAH a three-year, placebo-controlled trial. *Arthritis Rheum* 2001; 44: 2539-47.
8. SOLOMON L: Patterns of osteoarthritis of the hip. *J Bone Joint Surg* 1976; 58: 176-83.
9. LEDINGHAM J, DAWSON S, PRESTON B, MILLIGAN G, DOHERTY M: Radiographic patterns and associations of osteoarthritis of the hip. *Ann Rheum Dis* 1992; 51: 1111-6.
10. LIEVENSE AM, BIERMA-ZEINSTRE MA, VERHAGEN AP, VERHAAR JAN, KOES BW: Prognostic factors of progress of hip osteoarthritis. A systematic review. *Arthritis Care Res* 2002; 47: 556-62.
11. LEQUESNE MG, MERY C, SAMSON M, GERARD P: Indexes of severity for osteoarthritis of the hip and knee. Validation-value in comparison with other assessment tests. *Scand J Rheumatol* 1987; 65 (Suppl.): 85-9.
12. LEQUESNE M, LAREDO JD: The "faux profil" (oblique view) of the hip in the standing position. Contribution to the evaluation of osteoarthritis of the adult hip. *Ann Rheum Dis* 1998; 57: 676-81.
13. CONROZIER T, SAXNE T, SHAN SEI FAN C *et al*.: Serum concentrations of cartilage oligomeric matrix protein and bone sialoprotein in hip osteoarthritis: a one year prospective study. *Ann Rheum Dis* 1998; 57: 527-32.
14. CONROZIER T, TRON AM, MATHIEU P, VIGNON E: Quantitative assessment of radiographic normal and osteoarthritic hip joint space. *Osteoarthritis Cartilage* 1995; 3 (Suppl. A): 81-7.
15. CONROZIER T, LEQUESNE M, FAVRET H, TACCOEN A, VIGNON M, VIGNON E: Mea-

surement of the radiological hip joint space width. An evaluation of various methods of measurement. *Osteoarthritis Cartilage* 2001; 9: 281-6.

16. CONROZIER T, CHAPPUIS-CELLIER C, RICHARD M, MATHIEU P, RICHARD S, VIGNON E: Increased serum C-reactive protein levels by immuno-nephelemetry in patients with rapidly destructive hip osteoarthritis. *Rev Rhum* (Engl. ed) 1998; 65: 759-65.
17. NETZEL-ARNETT S, MALYA SK, NAGASE H, BÜKEDAL-HANSEN M, VAN WART HE: Continuously recording fluorescent assays optimised for five human matrix metalloproteinases. *Annal Biochem* 1991; 191: 86-92.
18. CLARK IM, POWELL LK, WRIGHT JK, CAWSTON TE: Polyclonal and monoclonal antibodies against tissue inhibitor of metalloproteinases (TIMP) and the design of an enzyme linked immunosorbent assay to measure TIMP. *Matrix* 1991; 11: 76-85.
19. TENGBLAD A: Quantitative analysis of hyaluronate in nanogram amounts. *Biochem J* 1980; 185: 101-5.
20. HARVEY S, WEISMAN M, O'DELL J *et al*.: Chondrex: new marker of joint disease. *Clin Chem* 1998; 44: 509-16.
21. WINTERBOTTOM N, VERNON S, FREEMAN K, DANILOFF Y, SEYEDIN A: A serum immunoassay for the C terminal propeptide of type I collagen. *J Bone Miner Res* 1993: 8: S341.
22. ROSENQUIST C, FLEDELIUS C, CHRISTGAU S *et al*.: Serum crosslaps one-step ELISA. First application of monoclonal antibodies for measurement in serum of bone related degradation products from C-terminal telopeptide of type I collagen. *Clin Chem* 1998; 44: 2281-9.
23. VANDEN BERG WP: Osteophyte formation in osteoarthritis. *Osteoarthritis Cartilage* 1999; 7: 333.
24. ROSENBERG ZS, SHANKMAN S, STEINER G, KASTENBAUM D, NORMAN A, LAZANSKY M: Rapid destructive osteoarthritis: clinical, radiographic and pathologic features. *Radiology* 1992; 182: 213-6.
25. DOUGADOS M, GUEGUEN A, NGUYEN M *et al*.: Radiographic features predictive of radiographic progression of hip osteoarthritis. *Rev Rhum* [Engl. ed.] 1997; 64: 795-803.
26. CONROZIER T, CARLIER MC, MATHIEU P *et al*.: Serum levels of YLK 40 and C reactive protein in patients with hip osteoarthritis and healthy subjects: a cross sectinal study. A*nn Rheum Dis* 200; 59: 828-31.
27. CHEVALIER X, CONROZIER T, GEHRMANN M *et al*.: TIMP-1 serum level may predict progression of hip osteoarthritis. *Osteoar - thritis Cartilage* 2001; 9: 300-7.
28. GARNERO P, CONROZIER T, CHRISTGAU S, MATHIEU P, DELMAS PD, VIGNON E: Urinary type II collagen C-telopeptide levels are increased in patients with a rapidly destructive hip osteoarthritis. *Ann Rheum Dis* 2003; 62: 939-43.
29. SPECTOR TD, HART DJ, NANDRA D *et al*.: Low-levels increase in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. *Arthri - tis Rheum* 1997; 40: 723-7.
30. VAN BEUNINGEN HM, VAN DER KRAAN PM, ARNTZ OJ, VAN DEN BERG WB: Differential effects of local application of BMP-2 and TGF-ß1 on both articular cartilage composition and osteophyte formation. *Osteoarthritis Cartilage* 1998; 5: 306-17.