

EXTENDED REPORT

Urinary CTX-II levels are associated with radiographic subtypes of osteoarthritis in hip, knee, hand, and facet joints in subject with familial osteoarthritis at multiple sites: the GARP study

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Ann Rheum Dis 2006;**65**:360–365. doi: 10.1136/ard.2005.040642

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Accepted 25 July 2005
Published Online First
11 August 2005

Objective: To assess the relation between the urinary concentrations of type II collagen C-telopeptide (UCTX-II) and radiographic signs of osteoarthritis (ROA) in the GARP (Genetics, Arthrosis and Progression) study.

Methods: UCTX-II levels were measured in GARP study participants, who are sibling pairs predominantly with symptomatic osteoarthritis at multiple sites. Kellgren and Lawrence scores were used to assess ROA in the knees, hips, hands, and vertebral facet joints, and spinal disc degeneration. A proportionate score was made for each joint location, based on the number of joints with ROA. The sum total ROA score represents a measure of cartilage abnormalities within each patient. By using linear mixed models the total ROA score and the joint site specific ROA scores were correlated with the UCTX-II level.

Results: In 302 subjects the mean (SD) and median (range) for UCTX-II were 265 (168) and 219 (1346) ng/mmol creatinine, respectively. There was a significant association between the total ROA score and UCTX-II levels. Subsequent multivariate analysis showed that the joint site specific ROA score at all joint sites, except for spinal disc degeneration, contributed independently to this association.

Conclusions: The total ROA score of GARP patients, representing cartilage abnormalities at the most prevalent ROA joint locations, showed an excellent correlation with UCTX-II levels. The specific ROA scores at the hip, hand, facet, and knee joints additively and independently explained this association. Even in patients with osteoarthritis at multiple sites, UCTX-II may be a sensitive quantitative marker of ROA.

Osteoarthritis is a disease characterised by degeneration of the articular cartilage and bone remodelling leading to pain and joint stiffness. The extend of osteoarthritis within each joint is usually assessed by radiographic characteristics and expressed as the Kellgren score.¹ However, a limitation of using radiographs to detect cartilage destruction is its lack of sensitivity: significant cartilage degradation must have occurred before it is visible on a radiograph.² Sensitive biochemical markers have been developed to detect overall cartilage degradation with more reliability and sensitivity, preferably at an early stage of the disease.^{3,4} Such markers may be useful for the early identification of patients with osteoarthritis and for assessing the response to treatment.⁵

One of the primary disease processes of osteoarthritis is degradation of the type II collagen (CII),⁶ which is most abundant and highly specific for cartilage tissue.⁷ In addition to the cartilage of synovial joints, collagen type II is also present in the nucleus pulposus and annulus fibrosus of the spinal discs.⁸ Measuring CII degradation fragments may thus be a specific marker of cartilage degradation occurring at both synovial joints and in the spinal discs, and may be more sensitive than the radiographic characteristics.^{9–11} Assays have been developed over several years that allow the CII degradation products to be detected.^{3,4,12} Most recently, immunoassays detecting C-terminal cross linking telopeptide of type II collagen (CTX-II) have been developed, and increased levels of CTX-II have been reported in synovial fluid soon after knee injury.¹³ In the urine, raised levels of CTX-II are associated with more rapid progression of

osteoarthritis and rheumatoid arthritis.^{12,14,15} In osteoarthritis, two recent cross sectional studies showed an association between the UCTX-II level and the presence of osteoarthritis and spinal disc degeneration. In a study of Reijman *et al*,¹⁶ it was shown that subjects within the highest quartile of UCTX-II levels have a four times increased risk of having radiographic signs of osteoarthritis (ROA) in the knee or hip and an increased osteoarthritis progression risk compared with the lowest quartile. Garnero *et al*¹⁷ showed that, in addition to knee and hand osteoarthritis, UCTX-II levels were independently influenced by lumbar spine disc degeneration.

None of these studies has data available on all major joints affected by osteoarthritis. Their results could therefore easily be confounded by cartilage degradation at other major joint locations for which radiographic data were lacking. The aim of the current study was to investigate whether, in subjects recruited to the GARP study (Genetics, Arthrosis and Progression), cartilage degradation occurring at each prevalent osteoarthritis joint location (knee, hip, hand, spinal facet joints, and disc degeneration) represented by a total ROA score was correlated with the UCTX-II level. Using multivariate analysis and a joint site specific ROA score, the independent contribution of each joint location to the UCTX-II level was investigated.

Abbreviations: CMC, carpometacarpal joint; CTX-II, C-terminal cross linking telopeptide of type II collagen; DIP, distal interphalangeal joint; GARP, Genetics, Arthrosis and Progression; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; ROA, radiographic signs of osteoarthritis; UCTX-II, urinary level of type II collagen C-telopeptide.

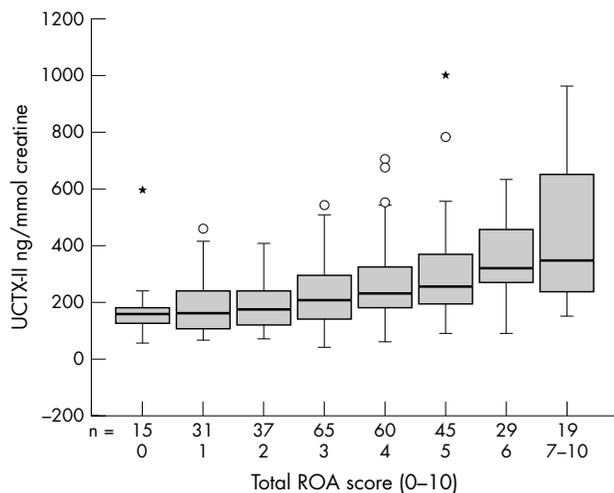


Figure 1 Box plot showing UCTX-II level in ng/mmol creatinine (not logarithmically transformed) for the increasing total ROA score (0–10). The box length represent the interquartile range (boundaries for 50% of the outcomes) with the thick horizontal line the median UCTX-II level. The vertical line represents the 5th and 95th centile. Circles are outliers (1.5 to 3 box lengths from the upper edge of the box) and stars are extremes (>3 box lengths from the upper edge of the box).

METHODS

The GARP study

The ongoing GARP study, which consists of white sibling pairs of Dutch ancestry affected predominantly by symptomatic osteoarthritis at multiple sites, is primarily aimed at identifying genetic determinants of osteoarthritis susceptibility and progression. Details of the ascertainment have been described elsewhere.¹⁸ Symptomatic osteoarthritis of a joint within the study was defined as having symptoms of osteoarthritis in addition to radiographic signs. Informed consent was obtained from all patients.

Proband (aged 40 to 70 years) and their siblings included in the GARP study had osteoarthritis at multiple joint sites of the hand, or symptomatic osteoarthritis in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip.¹⁸ Subjects with symptomatic osteoarthritis at only one joint site were required to have structural abnormalities in at least one other joint site, defined by the presence of ROA in either hip, knee, hand, or spine, or the presence of two or more Heberden nodes, Bouchard nodes, or squaring of at least one carpometacarpal (CMC) joint on physical examination.

Conventional radiographs of the hands (dorso-volar), knees (posterior-anterior (PA) in weight bearing/semiflexed,

and lateral), hips (PA), lumbar (PA and lateral) and cervical spine (anterior-posterior, lateral, and transbuccal) were obtained of all participants. This was done in a standard manner with a fixed film focus distance and a fixed joint position. Radiographic characteristics of osteoarthritis were defined according to Kellgren and Lawrence.¹ Definite ROA at a particular joint site was defined as a Kellgren score of 2 or higher. Symptoms of osteoarthritis were defined as pain in the particular joint on most days of the previous month, which is in accordance with the American College of Rheumatology (ACR) recommendations.^{19–21} Radiographic and symptomatic osteoarthritis scoring has been described in detail elsewhere.¹⁸ In the GARP study, seven and one subjects, respectively, had undergone unilateral and bilateral knee replacements, and 23 and 15, respectively, unilateral and bilateral hip replacement. Based on these selection criteria, in all 191 sibling pairs were included.

In the current paper we defined a proportionate score for each joint location on the basis of the number of joints with ROA. As no collagen type II breakdown products (UCTX-II) are expected from arthroplastic joints, these were considered as Kellgren score = 0 in the analyses undertaken in this study. The specific ROA score for the hips and knees (0–2) represented no, unilateral, or bilateral ROA involvement of the joints. For hand and facet ROA and spinal disc degeneration, first a sum score was derived based on the number of joint sites with a Kellgren score of ≥2. The sum score of the hand ranged from 0–20, consisting of distal interphalangeal joint (DIP) 2–5, proximal interphalangeal joint (PIP) 2–5, interphalangeal joints 1, and carpometacarpal joint 1. For spinal facet joints the sum score ranged from 0 to 11 and was based on the cervical joints (0–6; that is, C1/C2–C6/C7) and lumbar joints (0–5; that is, L1/L2–L5/S1). For disc degeneration of the spine the sum score ranged from 0 to 10 and was based on degeneration in the cervical discs (0–5; that is, C2/3–C6/C7) and lumbar discs (0–5; that is, L1/L2–L5/S1). These sum scores were subsequently compressed to a score of 0 to 2 in order to be proportional to the ROA score for hip and knee. The hand ROA score (0 to 2) represents subjects with, respectively, 0–2, 3–6, and ≥7 hand joints affected. For facet joints the ROA score (0 to 2) represents subjects with, respectively, 0–3, 4–6, and ≥7 facet joints affected. For spinal disc degeneration the score (0 to 2) represents subjects with disc degeneration at, respectively, 0–2, 3–5, and ≥6 levels. The total ROA score (0 to 10) comprised the sum of the joint site specific ROA scores that may represent a score proportional to cartilage abnormalities at each joint locations. For the 360 GARP subjects, ROA score data were available for all five joint locations evaluated.

The GARP study consists of 382 subjects (312 women and 70 men). Of the women, 260 (83%) were postmenopausal, including eight who were currently using hormone

Table 1 Characteristics and (frequencies) of ROA among sibling pairs in the GARP study

	GARP study	Hip	Knee	Hand	Facet	DD
Characteristics†	382 (1.0)	115 (0.30)	150 (0.40)	301 (0.79)	379 (0.99)	344 (0.99)
ROA score 0 (freq)‡		293 (0.77)	236 (0.62)	162 (0.45)	139 (0.39)	118 (0.33)
ROA score 1 (freq)‡		60 (0.16)	89 (0.23)	106 (0.30)	163 (0.45)	170 (0.47)
ROA score 2 (freq)‡		29 (0.08)	56 (0.15)	93 (0.26)	59 (0.16)	73 (0.26)
Age (SD)	60.3 (7.5)	62.5 (7.7)	61.8 (7.3)	61.3 (7.4)	60.3 (7.5)	60.9 (7.4)
BMI (SD)	27.0 (4.7)	26.5 (3.9)	28.1 (5.1)*	27.0 (4.5)	27.0 (4.7)	27.2 (4.7)
Women (freq)	312 (0.82)	83 (0.27)	122 (0.39)	244 (0.78)	309 (0.99)	279 (0.89)
Postmenopausal no HTR	252 (0.81)					

*p<0.05.

†Numbers represent patients within GARP with ROA in at least one site at the specific joint location including subjects with unilateral and/or bilateral joint replacement (n=38 for hip; n=8 for knee).

‡Proportional ROA scores were made based on the number of joint sites with ROA at each location. ROA scores of joint replacements were scored as ROA absent. BMI, body mass index; DD, spinal disc degeneration; GARP, Genetics, Arthrosis and Progression study; HRT, hormone replacement therapy; ROA, radiological osteoarthritis.

Table 2 Number and (frequencies) of subjects with ROA scores > 0 in at least 2 respective joint locations

	GARP study	Knee	Hand	Facet	DD
ROA scores	286 (0.95)*				
Hip		38 (0.13)	57 (0.19)	65 (0.23)	75 (0.26)
Knee			77 (0.25)	88 (0.29)	96 (0.34)
Hand				122 (0.40)	130 (0.43)
Facet					147 (0.51)

*ROA scores were available at all five sites in 286 of 302 individuals.

DD, spinal disc degeneration; GARP, Genetics, Arthrosis and Progression study; ROA, radiological osteoarthritis.

replacement therapy (HTR). As the menopause and HTR have recently been shown to influence urinary CTX-II levels,²² untreated postmenopausal women were selected (n = 252). The present study was undertaken in 234 untreated postmenopausal women, and 68 men for whom we had UCTX-II levels available.

Ethics approval

Any necessary ethics approval for the GARP study was secured by the committee medical ethics (CME) of the Leiden University Medical Centre.

Biochemical analysis

For each participant in the GARP study we have collected non-fasted second void morning urine samples which were stored within four hours at -80°C until measurement of urinary CTX-II was undertaken. Urinary CTX-II was measured by Synarc (Lyon, France) using an enzyme linked immunosorbent assay based on a monoclonal antibody raised against the EKGDPD linear 6-amino acid epitope of the CII C-telopeptide (CartiLaps, Nordic Bioscience, Herlev, Denmark). Intra-assay and interassay variation was less than 9% and 11%, respectively.

Statistical analysis

In order to assess the contribution of the joint site specific ROA scores and the total ROA score to the UCTX-II level as the study outcome, a mixed model regression analysis was undertaken using SPSS version 11 (SPSS, Chicago, Illinois, USA) with the UCTX-II level as the dependent variable and either the total ROA score as a quantitative measure or the specific ROA scores as defined above in the knee (0–2), hip (0–2), hand (0–2), facet (0–2), and spinal disc degeneration (0–2) as covariables. In the mixed model analysis we used family identity numbers (representing family relations) as random effect variables in order to model the familial dependencies that might occur for the UCTX-II level. Results of the mixed model analyses are expressed as estimates (β) which represent the association between increasing ROA grades and UCTX-II level.

In order to assess the risk of ROA at a given UCTX-II level, a logistic and ordered logit regression analysis was carried out with the ROA scores as the dependent variable and the UCTX-II levels divided into quartiles as the categorical variable. For the logistic regression analysis the dependent joint site specific ROA scores of knee, hip, hand, facet, and spinal disc degeneration were dichotomised by pooling ROA score grades 1 and 2, while the total ROA scores for the ordered logit regression analysis were categorised into four groups: total ROA score grade 0–2 (n = 99) as group 1, grade 3 (n = 64) as group 2, grade 4–5 (n = 97) as group 3, and grade 6–10 (n = 45) as group 4. In these analyses standard errors were estimated from the variance between sibling pairs (robust standard errors)²³ using StataSE8 software (Stata Corporation, College Station, Texas, USA) to adjust for the familial dependencies that might occur for the UCTX-II level.

The outcomes of all analyses are presented with the 95% confidence intervals (CI) and adjusted for age (years), body mass index (BMI in kg/m^2), and sex because these variables have previously been shown to be associated with both osteoarthritis and CTX-II levels.²² Familial aggregation of the UCTX-II level was estimated by comparing twice the between-sibling variance divided by the total variance. Because UCTX-II levels were not normally distributed, data were logarithmically transformed in the analyses.

RESULTS

Table 1 shows the characteristics from the GARP study. In the GARP study, 82 per cent of the patients included were female and disc degeneration and facet ROA of the spine especially were very prevalent. Sibling pairs were selected for the concomitant presence of osteoarthritis at hip, knee, hand or spine (see Methods), which is reflected by the numbers of individuals with an ROA score of >0 at different combinations of joints (table 2). In 302 subjects (postmenopausal women (n = 252) and men (n = 68)) the mean (SD) and median (range) UCTX-II level was, respectively, 265 (168) and 219 (1346) ng/mmol creatine; although the respective values among women were higher than among men, at 271 (175) and 219 (1335) v 242 (137) and 216 (657) ng/mmol creatine, this difference did not reach statistical significance (Mann–Whitney U test, $p = 0.34$). As shown in fig 1, a positive correlation between raw UCTX-II levels and increasing total ROA score (ranging from 0–10) was observed.

In order to investigate the extent and significance of the positive association between the total ROA score and the UCTX-II level measured, a mixed model was fitted. Using logarithmically transformed UCTX-II levels as the dependent variable and the total ROA score as the independent variable a significant positive association was observed, with an estimate 0.06 (95% CI, 0.04 to 0.07); $p = 0.0001$ (table 3). The heritability estimate of the UCTX-II level was 0.33 (NS), indicating a minor familial component influencing the UCTX-II level in this study group.

In order to investigate which joints contributed most to this association, multivariate mixed model analysis was subsequently performed with the joint-site specific ROA scores, knee (0–2), hip (0–2), hand (0–2), facet (0–2) and spinal disc degeneration (0–2).

As shown in table 3, for each of the joint groups except for intervertebral disc degeneration a significant independent contribution to increased UCTX-II levels could be detected. The highest estimate (0.11 (95% CI, 0.07 to 0.15)) was observed for hip ROA. Age and BMI did not influence the UCTX-II level; however, for women a significantly higher UCTX-II level ($p = 0.03$) was observed independent of the presence of ROA. The relative contribution of the joint location to the UCTX-II level was similar in men and women.

ROA risk associated to UCTX-II levels in GARP

To assess the ROA risk associated with the UCTX-II level among subjects in the GARP study, relative risks expressed as

Table 3 Mixed model analysis of UCTX-II and the total ROA score (grade 0–10) and multivariate to ROA scores (grade 0–2) of hip, knee, hand, facet and spinal disc degeneration

ROA scores	Median UCTX-II* (range)	Estimate† (95% CI)	p Value
Total 0 to 10 (n = 301)	219 (1346)	0.06 (0.04 to 0.07)	0.0001
Hip grade 0 (n = 228)	201 (1346)		
Hip grade 1 (n = 48)	288 (909)	0.11 (0.07 to 0.15)	0.0001
Hip grade 2 (n = 26)	325 (639)		
Knee grade 0 (n = 183)	210 (957)		
Knee grade 1 (n = 70)	233 (483)	0.05 (0.01 to 0.08)	0.011
Knee grade 2 (n = 48)	275 (878)		
Hand grade 0 (n = 129)	188 (742)		
Hand grade 1 (n = 90)	226 (1329)	0.05 (0.02 to 0.09)	0.002
Hand grade 2 (n = 83)	290 (888)		
Facet grade 0 (n = 109)	182 (540)		
Facet grade 1 (n = 139)	245 (742)	0.07 (0.03 to 0.11)	0.001
Facet grade 2 (n = 54)	269 (1302)		
DD grade 0 (n = 91)	188 (652)		
DD grade 1 (n = 144)	219 (957)	0.03 (–0.01 to 0.06)	0.199
DD grade 2 (n = 67)	265 (1329)		

*Mean UCTX-II expressed in ng/mmol creatinine.

†Data were analysed using mixed model regression analyses with UCTX-II levels logarithmically transformed as dependent variable and age, sex, body mass index, and the presence of ROA scores as covariables. Family identity numbers were added as a random effect variable to adjust for possible familial dependencies of the UCTX-II levels between siblings.

CI, confidence interval; DD, spinal disc degeneration; ROA, radiographic osteoarthritis; UCTX-II, urinary level of type II collagen C-telopeptide.

the odds ratio (OR) were calculated for the presence of ROA at a specific joint site, or for the total ROA score for subjects located within the different UCTX-II quartiles. Table 4 shows that subjects within the highest UCTX-II quartiles had an increased risk of having both ROA at a specific joint site and a higher grade of total ROA score. Subjects within the highest UCTX-II quartile show a significantly higher OR for hip ROA compared with those in the lowest quartile (OR = 7.7 (95% CI, 3.0 to 19.7)). Furthermore, subjects within this quartile also had a substantial risk of having ROA at other joint locations (OR = 7.7 (95% CI, 4.0 to 14.8)). For spinal disc degeneration we did not find such associations.

DISCUSSION

Primary osteoarthritis is a common disorder for which a wide variety of phenotypic definitions have been described. These definitions differ on the basis of either radiographic or symptomatic features of osteoarthritis, or in the distinction between the specific joint locations affected. In the GARP patients, there is a clear relation (table 1) between the presence of osteoarthritis at articular joints and spinal disc degeneration. As the nucleus pulposus and the annulus fibrosus of spinal discs both contain collagen type II, the presence of disc degeneration should be considered when measuring a collagen type II degradation marker. The current study is the first to investigate the relation between cartilage degradation, measured as the UCTX-II level, and the

concomitant occurrence of ROA at all prevalent joint locations—that is, the hip, knee, hand, and spinal facet joints as well as intervertebral disc abnormalities (table 2). A mean and median UCTX-II level of, respectively, 265 and 219 ng/mmol creatinine was measured among subjects in the GARP study. As expected for a study group selected for the presence of osteoarthritis at multiple joint sites, this level appears higher than the median level observed in recent studies by Reijman *et al*¹⁶ (median level 177 ng/mmol), which investigated the relation of UCTX-II levels and osteoarthritis within a population based sample, and Garnero *et al*,¹⁷ who found mean UCTX-II levels ranging from 166 to 299 ng/mmol in, respectively, subjects without and with intervertebral disc degeneration, knee ROA, and clinical hand osteoarthritis. Even within a group of subjects with symptomatic osteoarthritis at multiple joint sites (the GARP study), a highly significant association was observed between UCTX-II levels and the total ROA score (0.06; 95% CI, 0.04 to 0.07), indicating a significant and sensitive increase in UCTX-II level with increasing ROA scores occurring in the body. Subsequently, it was shown that ROA scores of the hip, knee, hand, and facet joints contributed independently to the UCTX-II levels, whereas spinal disc degeneration did not. The highest estimate (0.11; 95% CI, 0.07 to 0.15) was observed for hip ROA, indicating that the presence of ROA at this single joint site contributed significantly to the variation in the UCTX-II level. The fact that we did not observe an

Table 4 Logistic and ordered logit regression analysis to assess the risk of having ROA in relation to quartiles of UCTX-II level

UCTX-II quartiles (ng/mmol creatinine)	Adjusted OR (95% CI)*				
	Hip†	Hand†	Facet†	Knee†	Total ROA‡
44.3 to 147.4	1.0	1.0	1.0	1.0	1.0
147.4 to 218.9	2.3 (0.9 to 5.4)	1.3 (0.6 to 2.6)	1.2 (0.6 to 2.4)	1.2 (0.5 to 2.5)	1.5 (0.9 to 2.8)
218.9 to 328.1	5.6 (2.2 to 14.2)	2.4 (1.1 to 5.1)	2.1 (1.0 to 4.3)	1.5 (0.7 to 3.3)	4.3 (2.3 to 8.2)
328.1 to 1390.5	7.7 (3.0 to 19.7)	2.7 (1.3 to 5.8)	4.3 (1.9 to 9.7)	2.6 (1.2 to 5.7)	7.7 (4.0 to 14.8)

*Analysis were adjusted for age, body mass index, sex, and the presence of ROA in the joint sites that were not the dependent variable.

†The joint site specific ROA scores were dichotomised and used as the dependent variable in the logistic regression analysis.

‡The total ROA score was divided into four categories and used as the dependent variable in an ordered logit regression analysis.

CI, confidence interval; DD, spinal disc degeneration; OR, odds ratio; ROA, radiographic osteoarthritis; UCTX-II, urinary level of type II collagen C-telopeptide.

independent effect for spinal disc degeneration may either indicate that disc degeneration is a different pathophysiological process and, as such, does not contribute to the UCTX-II level, or that we were unable to detect its contribution owing to the concomitant occurrence of ROA at the other joint locations (table 2).

When exploring the value of the UCTX-II level as a biomarker for osteoarthritis, we showed that subjects within the highest UCTX-II quartile had a substantial risk of having ROA of the hip (OR = 7.7 (95% CI, 3.0 to 19.7)) in addition to a high risk of osteoarthritis at multiple joint sites simultaneously (OR = 7.7 (4.0 to 14.8)). These data indicate that when using the UCTX-II assay, subjects within the highest UCTX-II quartile (levels above 328 ng/mmol creatine) may need assessment of ROA at the hip joint in addition to other joint locations.

The strength of the current study is that it involved a large, well characterised sample of subjects with osteoarthritis at multiple joint sites simultaneously. As a result, cartilage degradation, measured as UCTX-II level, could be related to a proportionate ROA score representing degenerative disease at the hip, knee, hand, and spinal facet joints, and to intervertebral disc abnormalities. Together these locations represent the major skeletal sites at which degenerative disease is prevalent. The results of our study did not, therefore, seem to be confounded by cartilage degradation at joint locations for which radiographic data were lacking. Although our UCTX-II measurement appeared sensitive among subjects with osteoarthritis at multiple joint sites simultaneously, the absence of radiographic data—for example on the shoulders and diarthroidal joints—may have caused some bias. Furthermore, the women of our study were mainly postmenopausal. Although the total ROA score made a significant contribution to the UCTX-II level, we were unable to make a robust estimation of the contribution of the joint site specific ROA scores to the UCTX-II level. Some of our findings may therefore not apply to younger women or to postmenopausal women receiving HTR.

Our results are in contrast to the recently demonstrated association between UCTX-II levels and disc degeneration in the lumbar spine in a study by Garnero *et al.*¹⁷ Although the scoring method was similar between the two studies, we did not analyse cervical and lumbar spine disc degeneration separately. It could therefore be argued that Garnero's study involved a different subset of spinal abnormalities, or that the sensitivity for detecting the contribution of disc degeneration differed between the studies. However, assessing disc degeneration separately in the cervical and lumbar discs, or changing the disc degeneration ROA score to different proportions in our study did not alter the outcome (results not shown). It is also possible that the differences between the studies reflected confounding by the absence of hip osteoarthritis data in Garnero's study.

In a recent study by Reijman *et al.*¹⁶ it was shown that subjects in the highest quartiles of UCTX-II levels had a substantially increased risk of having osteoarthritis in the knee or hip joints. However, in that study radiographic data on the hands, facet joints, and intervertebral disc degeneration of the spine were not taken into account. In view of the prevalence of hand and facet ROA, its correlation with knee ROA, and their relative strong effects on UCTX-II levels compared with knee ROA (table 3), it is possible that the risk for knee ROA in that study was somewhat overestimated.

From the results of the present study, we conclude that UCTX-II levels are strongly correlated with overall cartilage degradation occurring in the hip, hand, facet, and knee joints. We were unable to detect an independent effect for spinal disc degeneration. Further research is necessary to establish an association between UCTX-II levels and progression of osteoarthritis.

ACKNOWLEDGEMENTS

We would like to thank Mr M Bakker-Verweij for handling the urine samples. We acknowledge the support of the cooperating hospitals and referring rheumatologists, orthopaedic surgeons and general practitioners in our region for identifying eligible GARP patients, in random order: Dr L N J E M Coene, Department of Orthopaedic Surgery and Dr H K Ronday, Department of Rheumatology, Leyenburg Hospital, The Hague; I Speyer and Dr M L Westedt, Department of Rheumatology, Bronovo Hospital, The Hague; Dr D van Schaardenburg, Department of Rheumatology, Jan van Breemen Institute, Amsterdam; Dr A J Peeters and Dr D van Zeben, Department of Rheumatology, Reinier de Graaf Hospital, Delft; Dr E J Langelaan, Department of Orthopaedic surgery, Rijnland Hospital, Leiderdorp; and Dr Y Groeneveld, General Practitioner, associated with the Leiden University Medical Centre. We also acknowledge grant support from The Netherlands Organisation for Scientific Research (NWO No 904-61-095), and Pfizer Inc, Groton, Connecticut, USA, for their generous financial support for this work.

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