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Skin pentosidine in very early hip/knee osteoarthritis (CHECK) is not a strong independent predictor of radiographic progression over 5 years follow-up

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SUMMARY

Objectives: Age-related changes in articular cartilage are likely to play a role in the etiology of osteoarthritis (OA). One of the major age-related changes in cartilage is the accumulation of advanced glycation end products (AGEs). The present study evaluates whether pentosidine can predict radiographic progression and/or burden over 5 years follow-up in a cohort of early knee and/or hip OA.
Design: The 5 years follow-up data of 300 patients from cohort hip & cohort knee (CHECK) were used. Radiographic progression and burden were assessed by X-rays of both knees and hips (Kellgren and Lawrence (K&L) and Altman scores). Baseline pentosidine levels (and urinary CTXII as a comparator) were measured by high-performance-liquid-chromatography (HPLC) and enzyme linked immunosorbent assay (ELISA). Univariable and multivariable associations including baseline radiographic damage, age, gender, body mass index (BMI) and kidney function were performed.
Results: Both pentosidine and urinary C-terminal telopeptide of type II collagen (uCTXII) correlated with radiographic progression and burden. In general pentosidine did not have an added predictive value to uCTXII for progression nor burden of the disease. The best prediction was obtained for burden of radiographic damage ($R^2 = 0.60–0.88$), bus this was predominantly determined by baseline radiographic damage (without this parameter $R^2 = 0.07–0.17$). Interestingly, pentosidine significantly added to prediction of osteophyte formation, whereas uCTXII significantly added to prediction of JSN in multivariable analysis.
Conclusion: Pentosidine adds to prediction of radiographic progression and burden of osteophyte formation and uCTXII to radiographic progression and burden of JSN, but overall skin pentosidine did not perform better that uCTXII in predicting radiographic progression or burden. Burden of damage over 5 years is mainly determined by radiographic joint damage at baseline.

Introduction

The pathogenesis of osteoarthritis (OA) is unknown. Several risk factors are described, age being clearly one of the main factors. A major age-related change in articular cartilage is the modification of proteins by non-enzymatic-glycation (NEG). NEG is a common posttranslational modification of proteins caused by reducing sugars. The spontaneous condensation of reducing sugars with free amino groups in lysine or arginine residues on proteins leads *via* Schiff bases, Amadori rearrangement, and Maillard reactions subsequently into advanced glycation end products (AGEs)[1]. As such, NEG can result in adducts to a protein, changing its properties[2], but also in the formation of cross-links between proteins, changing the integrity of the cartilage matrix[3].

AGEs are only removed from tissues when the proteins involved are degraded and removed. Cartilage tissue has a low turnover of its proteins resulting in abundant AGE accumulation[3,4] over the years. As such these AGEs may be the intermediate in age-related predisposition to OA.

In vitro investigations show that AGEs have a negative influence on mechanical[3,5] and biochemical[2,6] properties of the cartilage tissue making it more prone to mechanical damage. *In vivo* effect of AGEs has

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been investigated in several models. In the anterior cruciate ligament transaction (ACLT) model artificial elevated AGE levels of the joint cartilage leads to an increase in progression of OA compared to joints without elevated AGE levels[7]. Upon minimal applied surgical damage of the cartilage according to the canine Groove model[8] in combination with restricted joint loading, artificial increase of AGE levels shows a tendency to more severe OA progression[9].

To further understand the role of AGEs in specifically human OA, ideally cartilage biopsies would be used to assess AGE levels and relate those to OA development and/or progression in longitudinal study designs. The drawback of such an approach is – amongst others – the possibility of interfering with the disease process (the cartilage biopsy may induce and/or accelerate OA development). An alternative and more feasible approach might be the use of the AGE characteristics of another, more accessible, connective tissue with relative low turnover, such as skin, as a surrogate for the AGE characteristics of cartilage. AGE accumulation with increasing age in skin collagen is linearly correlated to accumulation in cartilage[4,10]. Cartilage pentosidine is about five times higher compared to skin pentosidine[10]. When using skin pentosidine as a surrogate marker for cartilage pentosidine in a cross sectional study on early radiographic OA, skin pentosidine is increased in patients with mild OA compared to those without OA[10]. Urine CTXII is from all biomarkers reported on thus far, the one that best relates to development and progression of OA[11–13]. Moreover, this biomarker has already been proven applicable in clinical trials to monitor disease activity and to decide on treatment of rheumatoid arthritis[14]. As such this biochemical marker is a relevant comparator in case of studies on biochemical markers of joint damage.

Up till now plain radiographs are the gold standard for imaging hip and knee joint damage. These radiographs can be scored in different ways. The K&L classification[15] is probably the most used one. This method uses joint space narrowing (JSN), osteophyte formation, and subchondral sclerosis in a combined score, whereas the Altman atlas score[16], scores these features independently. Both these methods use a stepwise scoring (ordinal variable) (e.g., 0–4 for K&L and max 0–3 for JSN for Altman).

In a cross sectional study we showed in a cohort of patients with very early signs of knee and/or hip OA (CHECK) that skin pentosidine was higher in participants with more severe radiographic joint damage as calculated by the sum of the K&L score of both hips and knees[10]. The present study describes whether these skin pentosidine levels are useful to predict progression of OA over 5 years follow-up, compared to/or in addition to uCTXII, also taking demographic and radiographic baseline characteristics into account.

Methods

Cohort description

Three-hundred participants from the Dutch CHECK cohort ('cohort hip & cohort knee') were asked to participate. Participants were included with pain and/or stiffness in hip and/or knee, aged 45–66 years, and never or no longer than 6 months had visited the general practitioner for these complaints. Participants with a known rheumatic condition, and Kellgren and Lawrence grade IV of hip and/or knee were excluded. For details see Wesseling *et al.*[17] This study was approved by medical ethical committee of the University Medical Centre (UMC) Utrecht and according to the declaration of Helsinki. All participants gave written informed consent.

Skin pentosidine as surrogate markers of cartilage AGE

At baseline a full-thickness punch skin biopsy (4 mm Ø) was taken from the lower back according to standard procedures[10]. Pentosidine was used as a measure of the various AGEs formed. It is reported that pentosidine represents a number of AGE markers such as N^{ε}-(carboxymethyl)lysine and N^{ε}-(carboxyethyl)lysine[18]. Pentosidine in the skin was measured by high-performance-liquid-chromatography (HPLC) as described previously and the pentosidine content of collagen samples is expressed as mmol/pmol collagen[19].

Cartilage breakdown marker; uCTXII

uCTXII as a biomarker supposed for degradation of hyaline cartilage type II collagen but supposedly also involved in bone turnover[20], was measured by ELISA (CartiLaps, Nordic Bioscience, Denmark) according to manufacturer's guidelines. Intra-assay and inter-assay variation of the same sample were both $\leq$10%. Urinary uCTXII values were normalized by urinary creatinine (Johnson & Johnson Vitos 250 Clinical Chemistry Slides) to account for urinary dilution. uCTXII is expressed as ngram/mmol creatinine.

Kidney function

As a potential confounder, kidney function was determined since it might be related to skin pentosidine level and uCTXII due to the fact that less excretion of plasma pentosidine and CTXII in kidney dysfunction is seen[21] and might also be related to more severe disease. Creatinine in peripheral blood was measured by Unicel DxC 800, Beckman Coulter (Fullerton, CA, USA). Estimated glomerular filtration rate was calculated by the Cockroft–Gault formula[22].

Radiographic joint damage

Radiographs of both knees and hips were taken from all participants. Radiographs of tibio-femoral (TF) joints were made by a weight-bearing posterior anterior view, and semi-flexed (7–10°) according to Buckland-Wright[16,23,17]. For the hip, weight-bearing anterior posterior radiographs of the pelvis were made[24].

Radiographs of both knees and hips were obtained at baseline (T0) and after 2 and 5 years (T2 and T5). All radiographs were scored according to K&L[15] with all three time points in view at the same time, and known sequence.

Radiographic OA burden was expressed as the summed K&L grade of both hips and knees. When a prosthesis was implanted (in 12 cases) the score + 1 (unless already maximum) of the latest time point was used. Total scores were calculated by taking the sum of the individual scores of the four joints leading to a maximum score of 16. Also the different radiographic features were scored by using the Altman atlas[16]. The Altman score provides scores of the joint space narrowing (JSN; 0–3) at two places for the knees and two for the hips. The sum of these scores was used to measure the overall JSN of four joints (max. 24). The osteophyte formation is scored on four different places in the knee as well as the hip (0–3 except for acetabulum inferior 0–1). The sum of these scores was calculated for a total score of the osteophyte formation of a patient (max 44).

Radiographic OA *progression* was expressed as the area under the curve (AUC) of the summed K&L grade over the 5 years minus the baseline value over 5 years. The *burden* of radiographic joint damage was expressed as the AUC over 5 years. For the summed Altman scores for JSN and osteophyte formation the same approaches were used to determine *progression* and *burden* scores per patient.

Statistical analysis

Continuous variables were described using means with standard deviation (SD) or medians with twenty-fifth and seventy-fifth

percentiles where appropriate, categorical data were described using frequencies and percentages.

Skin pentosidine and uCTXII were divided in three equal groups (tertiles) and the radiographic progression and burden scores were compared between the group with the highest and the lowest biomarker level and tested using Mann–Whitney *U* tests.

Correlations of skin pentosidine levels as well as uCTXII levels with radiographic progression and burden scores were investigated by Pearson correlation.

Multivariable linear regression analyses were used to correct for possible confounders and investigate the additional predictive value of skin pentosidine/uCTXII above other predictors. In these analyses age, gender, creatinine clearance, and body mass index (BMI) as well as baseline radiographic scores were evaluated as covariables. These variables were used based on known confounders from the baseline analysis. Final models were defined using a backward selection strategy starting removing variables that were not statistically significantly (based on a change in the regression coefficient of >10%). Since we carefully decided on variables to include and outcomes to study and the plausibility of our results we decided not to adjust our *P* values for that and use the regular *P* value of 0.05.

A P value $\leq$ 0.05 was taken as statistically significant and all statistical analyses were performed using SPSS version 15.0.

Results

Characteristics of study population

The characteristics of the study population and of the radiographic progression are shown in Tables IA and IB, respectively. Sixty-five of the 300 participants did not contribute. In 61 cases radiographic data were not complete for all three time points and/or biochemical data were missing, so for 183 participants all data were available and these were used in the current analyses. In total nine participants reported to have diabetes. The baseline demographics (age, gender, BMI, and kidney function) and baseline radiographic characteristics did not differ statistically significant from the original 244 cohort patients. For all radiographic parameters statistically significant progression of OA was seen (Table IB).

Differences in radiographic progression and burden between low and high skin pentosidine as well as low and high uCTXII

To test whether patients with high vs low skin pentosidine/uCTXII levels at baseline had a different progression and/or total burden of radiographic OA over 5 years, the lowest and highest tertiles of skin pentosidine/uCTXII were compared for radiographic progression and burden scores (Fig. 1).

For skin pentosidine the AUC progression and burden sum K&L score showed no difference between patients with the highest and lowest tertile [Fig. 1(A)]. The same was found for AUC progression and burden Altman JSN [Fig. 1(B)]. For Altman osteophytes the AUC progression and burden were significantly higher in the group with high skin pentosidine [Fig. 1(C); $P = 0.001$ and 0.024, respectively].

For the highest and lowest uCTXII tertiles, AUC progression and burden scores [Fig. 1(D–F)] were all (except for one) statistically significant different, with the most severe damage scores for the highest uCTXII level. When the participants with low skin pentosidine and low uCTXII were compared with those for both parameters in the highest tertile ($n = 21$ and 17 for both lowest and both highest combined tertiles, respectively) all radiographic characteristics were more severe in the group with high compared to low combined pentosidine and uCTXII values [Fig. 1(G–I)] and differences became clearly more outspoken, suggesting additive predictive ability.

Table IA
The baseline characteristics of the study population

Variable		
Age (years)*	55.5 ± 5.4	45–66
BMI (kg/m^2)†	26.37	23.9–29.3
Gender (M/F)‡	30/153	
Skin pentosidine/collagen (mmol/mol)†	2.34	1.88–2.83
uCTXII (ngram/mmol)†	0.29	0.20–0.40
Creatinine clearance (ml/min/1.73 m^2)*	93.8 ± 22.1	52–170

* Mean values ± SD with min and max values.
† Median values with 25–75 percentiles.
‡ Actual numbers of patients.

Table IB
The radiographic characteristics at baseline and 5 years follow-up

	T0		T5		*P* value
	Mean ± SD	Min–max	Mean ± SD	Min–max	T0–T5
Sum K&L score	1.69 ± 1.13	0–4	3.30 ± 1.81	0–7	$P < 0.001$
Sum Altman JSN	3.40 ± 2.58	0–11	4.97 ± 3.02	0–14	$P < 0.001$
Sum Altman osteophyte	3.34 ± 3.01	0–15	6.47 ± 4.52	0–22	$P < 0.001$

Sum K&L score calculated by taking the sum of the individual scores of the four joints leading to a maximum score of 16. Sum Altman JSN and osteophyte scores are the sum of the scores of the different locations (2 and 4, respectively) in all four individual joints (max. 24 and 44, respectively). *P* values for Wilcoxon rank test are given.

Correlation of skin pentosidine and uCTXII with radiographic damage

In Table II correlations of skin pentosidine and uCTXII with radiographic progression and burden for the overall (K&L) and separate characteristics (JSN and osteophytes) are given. In general, correlations with radiographic progression and burden were stronger for uCTXII than for skin pentosidine. For uCTXII relations with radiographic burden were in general stronger than for radiographic progression. For skin pentosidine this was the other way around.

Figure 2 provides representative figures for skin pentosidine against sum K&L grade for progression and burden (A and B, respectively) and for uCTXII for sum Altman JSN for progression and burden (C and D, respectively).

Multiple regression analysis

In Table III different final regression models based on the multivariable linear regression analysis are shown. Regression coefficient and *P* values for the different independent variables in each of the models are given. In case of the models for AUC burden the R^2 for each model with and without baseline radiographic damage is given.

For the progression scores for all three radiographic outcome parameters (sum K&L, Altman JSN, and Alman osteophytes) the explained variance (R^2) was low, between 0.03 and 0.23. For the radiographic burden scores the R^2 is higher, between 0.69 and 0.88. Regarding burden, for all radiographic parameters, the baseline radiographic parameter was most strongly related to outcome as can be deduced from the high regression coefficient (as compared to the other variables in the models) and the significant decrease in explained variance when excluding these variables from the model (i.e., for burden K&L from 0.69 to 0.14). For all three radiographic parameters combining skin pentosidine with uCTXII in the models

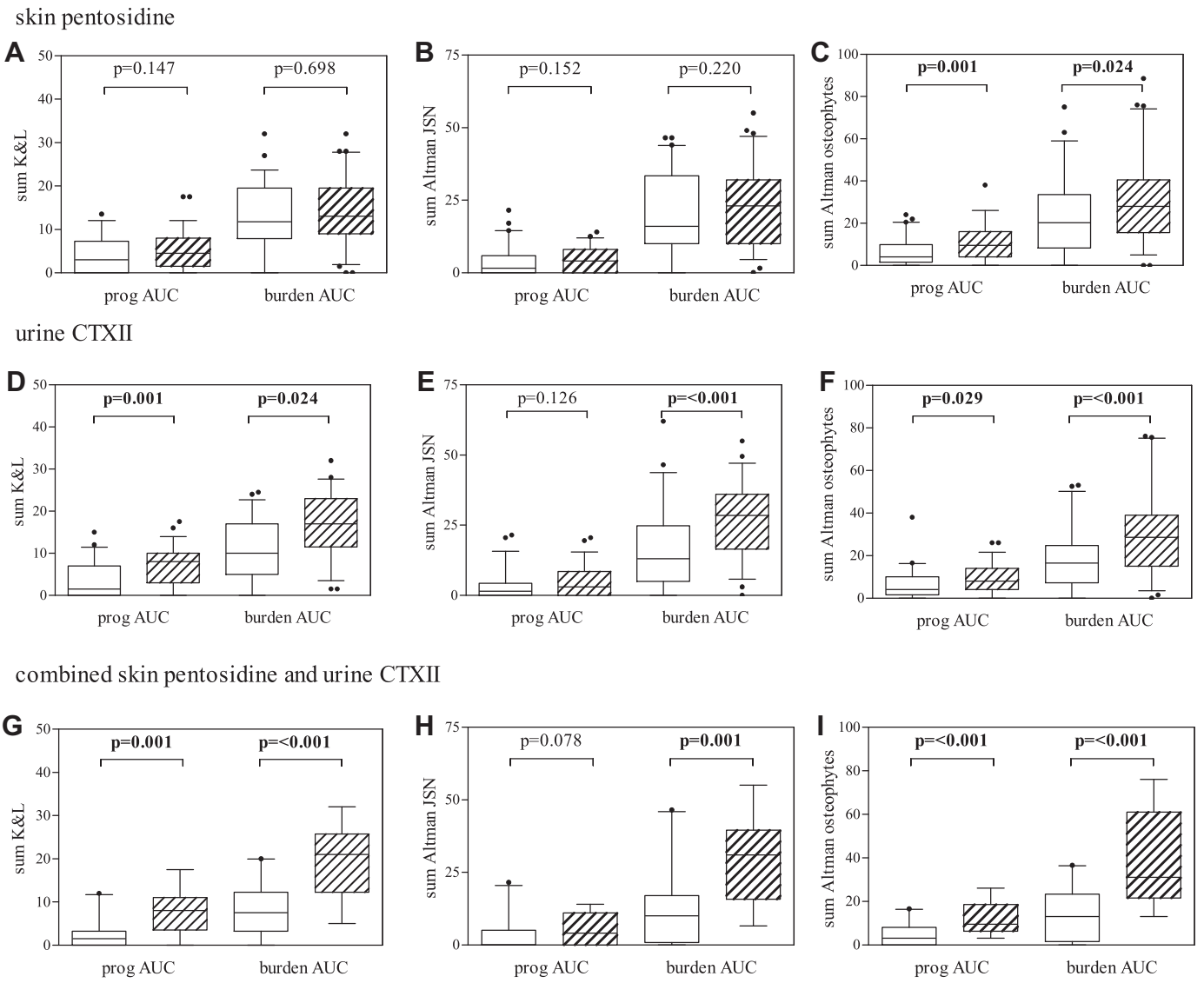

Fig. 1. Difference between progression and burden of radiographic OA for participants with low and high skin pentosidine, uCTXII or the combination. Participants with low (white) and high (dashed) tertiles skin pentosidine (A–C; $n = 66$ in the low and high group), urine CTXII (D–F; $n = 68$ and 67 in the low and high group respectively), and both (G–I; $n = 21$ and 17 in the low and high group, respectively) at baseline. Differences in sum K&L (A, D, G), sum Altman JSN (B, E, H), and sum Altman osteophytes (C, F, I) scores are given. Median (dash), with the interquartile range (box; 50%) with the fifth and ninety-fifth percentiles (whiskers) are presented. *P* values are indicated.

did not result in significant improvement of predictive ability of the model, supporting the dominant role of the baseline radiographic characteristics. In this analysis both skin pentosidine and uCTXII were predictive of sum K&L score, progression and burden. Interestingly, skin pentosidine did not (significantly) add to prediction of sum Altman JSN, whereas uCTXII did, for progression and burden. On the other hand skin pentosidine added to sum Altman osteophyte score but uCTXII did not, again both for progression and burden. In general BMI did not add to the model with uCTXII as independent biomarker variable but did add to the model with skin pentosidine as biomarker independent variable.

Table II
Correlations between skin pentosidine levels and uCTXII levels with radiographic progression of OA and burden of OA

	Skin pentosidine		uCTXII	
	R	*P*	*R*	*P*
Progression AUC				
Sum K&L	**0.167**	**0.024**	**0.323**	**<0.001**
Sum Altman JSN	0.123	0.095	**0.190**	**0.016**
Sum Altman osteophytes	**0.301**	**<0.001**	**0.194**	**0.014**
Burden (total) AUC				
Sum K&L	0.056	0.454	**0.360**	**<0.001**
Sum Altman JSN	0.113	0.127	**0.332**	**<0.001**
Sum Altman osteophytes	**0.180**	**0.015**	**0.290**	**0.001**

Statistical significant *P* values are given in bold.

Discussion

It was studied whether skin pentosidine better, alone or in combination with uCTXII can predict radiographic progression and burden of knee and hip joint damage very early in the osteoarthritic disease process. In general skin pentosidine could not improve the predictive ability of uCTXII for progression or burden of disease. The best predictive models were obtained for burden of radiographic damage, but this was predominantly determined by baseline radiographic damage. Skin pentosidine significantly added to prediction of osteophyte formation whereas uCTXII did not, and uCTXII significantly added to JSN whereas skin pentosidine did not.

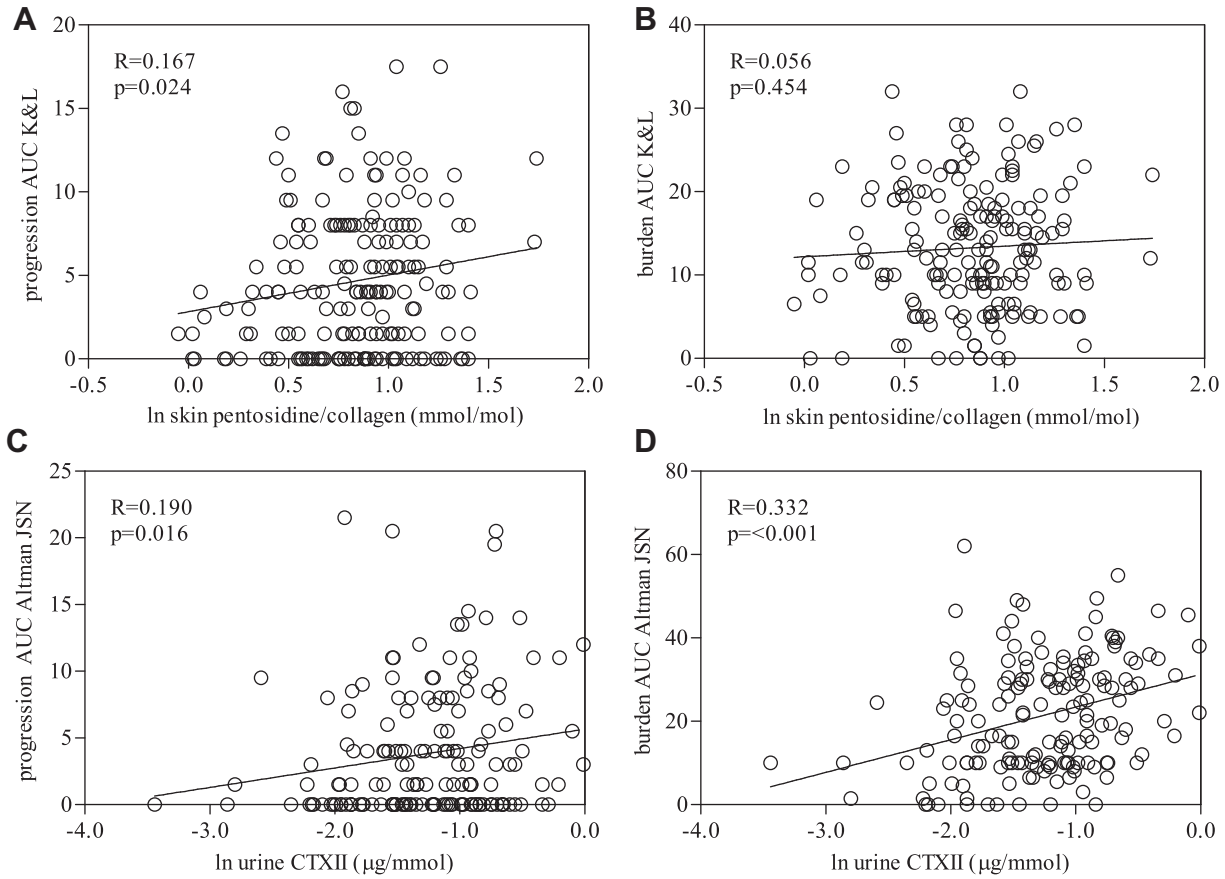

Fig. 2. Correlations skin pentosidine and uCTXII with parameters of radiographic progression and burden. For skin pentosidine the sum K&L scores for progression and burden (A and B, respectively) and for uCTXII the sum Altman JSN scores (C and D, respectively) are given as representative figures. Correlation coefficients with *P* values for all relations are given in Table II. Pearson correlation coefficients with *P* values are provided.

Previously we demonstrated in a cross sectional approach that skin pentosidine is higher in participants with more severe radiographic K&L hip and knee joint damage[10]. The present study demonstrates that for progression and burden of disease over 5 years this association is lost. On the other hand, uCTXII at baseline was discriminative for general (K&L) radiographic progression and burden. Interestingly, when osteophyte formation was evaluated as an independent radiographic characteristic, skin pentosidine was related to progression and burden over 5 years follow-up, whereas this is not the case for JSN. But in regression analyses, despite statistical significance, the explained variance was only marginally increased and insufficiently to aid to prediction of radiographic progression in individual patients. When the hips and knees were analyzed separately, in univariable analysis the hip OA is more associated with skin pentosidine and knee OA more with urine CTXII (Tables 2A and 2B, online). In multivariable analysis these minor differences became less pronounced (Tables 3A and 3B, online).

When studying skin pentosidine or uCTXII a different aspect of metabolism is studied. Skin pentosidine can be used to get more insight in cartilage pentosidine levels[4]. The rate of collagen turnover in skin is around 14.8 years, and even longer in cartilage[4], resulting in accumulation of pentosidine over time into the tissue. When using skin pentosidine in relation to radiographic damage the effect of AGEing on OA during lifetime is investigated. uCTXII level is a marker for cartilage degeneration[11], at a certain point in time and no cumulative measure as tissue pentosidine levels are. CTXII is mostly detected in areas with collagen type II damage, but also close to the bone suggesting that CTXII can be associated with subchondral bone changes[20,25]. Moreover, pentosidine is studied to be causative in joint degeneration, whereas uCTXII is the result of joint degeneration. Irrespectively, skin pentosidine was compared to uCTXII as uCTXII is at present suggested to be the best predictor of radiographic joint damage in OA[11,12]. In case skin pentosidine would be of use as a predictor, its predictive ability should out reach that of uCTXII. This is of even more importance regarding the invasiveness of taking skin biopsies followed by complex HPLC analysis in comparison to analyzing a urine sample by ELISA. This means that in clinical practice uCTXII is much easier to use. In case skin pentosidine would have been a good predictor, alternative and less invasive measurement for skin pentosidine such as skin auto fluorescence measurement[26] could have been enhanced and studied.

Despite the difference in both markers and the difference in their predictive ability, osteophytes and JSN, respectively, they hardly contributed to each other in predicting radiographic progression. For burden this is reasonably explained by the large predictive ability of baseline radiographic damage, for progression this remains speculative.

For skin pentosidine the strongest relation with JSN was expected since pentosidine formation negatively influences the biochemical and biomechanical aspect of the cartilage tissue[27]. However the strongest relation was observed with osteophyte formation. Osteophytes probably don't have a direct role in disease progression but may serve as markers of the location and severity of the pathologic process[28]. Cartilage can have focal damage not influencing joint space on radiographs yet. In this early phase osteophytes may already be formed at the areas with focal damage and can be seen earlier on radiographs than JSN.

Table III
Multivariable analysis for skin pentosidine and uCTXII as well as the combination, with radiographic progression and burden as dependent variable.

	Skin pentosidine			uCTXII			Combination		
	B	*P*	R^2	*B*	*P*	R^2	*B*	*P*	R^2
K&L progression AUC									
Skin pentosidine	1.74	0.01		NA	NA				
uCTXII	NA	NA		2.5	<0.001		2.5	<0.010	
Age	0.11	0.10							
BMI	4.48	0.03							
K&L burden AUC									
Skin pentosidine	2.5	0.01		NA	NA		1.7	0.10	
uCTXII	NA	NA		2.5	<0.001		2.5	<0.001	
BMI	4.2	0.05	0.14			0.17			0.17
Baseline rad.	5.4	<0.001	**0.69**	5.0	<0.001	**0.67**	5.1	<0.001	**0.68**
JSN progression AUC									
Skin pentosidine	0.6	0.05		NA	NA				
uCTXII	NA	NA		0.5	0.02		0.5	0.02	
BMI	1.1	0.09							
JSN burden AUC									
Skin pentosidine				NA	NA				
uCTXII	NA	NA	0.07	1.7	<0.001	0.10	1.7	0.02	0.10
Baseline rad.	4.9	<0.001	**0.87**	4.8	<0.001	**0.88**	4.8	<0.001	**0.88**
Osteophytes progression AUC									
Skin pentosidine	1.1	<0.001		NA	NA		1.0	0.02	
uCTXII	NA	NA							
BMI	2.3	<0.001		2.4	0.01		1.9	0.02	
Baseline rad.	0.6	<0.001		0.6	<0.001		0.6	<0.001	
Kidney function	−0.01	0.09		−0.01	0.10				
Osteophytes burden AUC									
Skin pentosidine	0.6	0.01		NA	NA		0.5	0.01	
uCTXII	NA	NA							
BMI	0.9	0.03	0.08			0.12	0.9	0.07	0.11
Baseline rad.	2.1	<0.001	**0.85**	2.1	<0.001	**0.83**	2.0	<0.001	**0.85**

Regression coefficient and *P* values are given for the variables in each model. The explained variance (R^2) for the AUC progression models for all three outcome parameters (sum K&L, Altman JSN, and Altman osteophytes) is low: between 0.03 and 0.23. For the models AUC burden explained variance (R^2) for the whole model (bold) and the whole model but excluding baseline radiographic data is given, clearly demonstrating the contribution of baseline radiographic damage to the model. Age, BMI, baseline radiographic characteristics, kidney function, and gender were added as independent covariables, and removed from the model when not contributing.

Synovial inflammation often occurs in OA, in early as well as advanced disease. The synovium can be involved in bone matrix remodeling, synovial macrophages can differentiate to form functional osteoclasts capable of bone remodeling[29]. Inflammatory activity adds to this process[30]. AGEs can activate receptor for advanced glycation endproducts (RAGE) and stimulate chondrocytes and synoviocytes in the production of pro-inflammatory cytokines[31]. Osteophyte formation has been related to synovial inflammation[32]. The question is whether AGEs are responsible for early osteophyte formation through inflammation and so this mechanism can explain the relationship between skin pentosidine and osteophytes progression and burden.

BMI is associated with OA and AGEs, so BMI was included in the final model. Because not the main focus we did not in further detail evaluate the association between BMI and AGE. Diabetes is also a known to be related to AGE formation. In our cohort we have a low number of participants with reported diabetes. When adding this into the final model no significant changes were seen and diabetes was not related to OA in our study. Because of the uncertainty about the actual number of diabetes patients (it was not tested for) these data are not included in the results.

For the radiographic burden baseline radiographic damage was clearly the best predictive of all variables far out reaching that of uCTXII or skin pentosidine. When this parameter was excluded the explained variance of the burden of radiographic damage with the other independent variables decreased enormously. For both the hip and knee earlier investigations showed that baseline radiographic parameters are associated with progression of OA[33,34]. As such this observation fits very well with the present knowledge.

In conclusion: Skin pentosidine adds to prediction of radiographic progression and burden of osteophyte formation and uCTXII to radiographic progression and burden of JSN, but overall skin pentosidine did not perform better than uCTXII in predicting radiographic damage, and baseline radiographic damage was far out the best predictor of radiographic burden. Neither of both biochemical markers is sufficiently discriminating to aid to prognosis of radiographic progression in individual patients, nor performs so consistently that it could function as an outcome in clinical trials.

Authors' contributions

All authors participated in the conception, design and analyses of the study.

Ethics approval

The study was approved by the medical ethics committees of all participating centers.

Conflict of interest

None.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2013.03.006.

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