Serum levels of matrix metalloproteinase-3 as a prognostic marker for progression of cartilage injury in patients with knee osteoarthritis

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ABSTRACT

Objective: To evaluate serum matrix metalloproteinase (MMP)-3 levels as a prognostic marker for the progression of cartilage damage in patients with knee osteoarthritis (KOA).

Methods: Fifty-six patients who met the ACR criteria for KOA, were included in a one-year observational prospective clinical study. Complete baseline and follow-up data were collected from 50 out of 56 patients. X-ray and magnetic-resonance images were carried out at baseline and after 12 months. They were evaluated according to the Kellgren-Lawrence and Whole-Organ magnetic Resonance iMaging Score (WORMS) semi-quantitative scales, respectively. Progression of cartilage damage in the medial tibiofemoral compartment was registered at the end of the follow-up using the change in WORMS. Serum levels of MMP-3 were measured during the baseline visit, using enzyme-linked immunosorbent assay.

Results: Significantly higher values of baseline MMP-3 levels were observed in patients with a registered progression of cartilage injury in the medial tibiofemoral compartment of the knee compared with patients with no progression (p = 0.005). Binary logistic regression analysis showed that levels of serum MMP-3 (ng/ml) were an independent predictor of subsequent progression of cartilage injury in the medial tibiofemoral compartment of the index knee (assessed by MRI) (OR = 1.042, CI 95%: 1.002-1.084). Receiver operating characteristic analysis was performed to separate progressors from non-progressors.

Conclusion: Serum MMP-3 levels may serve as a potential prognostic biomarker for cartilage injury in patients with KOA.

Keywords: Osteoarthritis; Knee; Cartilage; Biomarkers; Matrix Metalloproteinases

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INTRODUCTION

Matrix metalloproteinases (MMPs) are a large family of extracellular zinc-dependent endopeptidases that catalyze the production and degradation of extracellular matrix (ECM) under both physiological and pathological conditions[1]. Seven MMPs have been shown to be expressed under certain circumstances in articular cartilage, three among them (MMP-3, MMP-8, and MMP-9) appearing to be characteristic of pathologic circumstances only[2,3].

MMP-3 is the main MMP family member involved in cartilage degradation and is considered to possess some unique characteristics. Enhanced by interleukin-1[4], it possesses a broad substrate specificity enabling to be active against types II, III, and IV collagens, gelatin, laminin, proteoglycans, fibronectin, and fibulin-3[5,6]. Additionally, MMP-3 is able to activate MMP-1, MMP--2, MMP-9, and MMP-13[7,8].

Serum levels of MMP-3 are elevated in a number of inflammatory rheumatic conditions, characterized by joint synovitis, including rheumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis, and acute crystal arthritis, reflecting synovial inflammation[9]. A recent study has been published to show that MMP-3 levels may be a prognostic factor for rheumatoid arthritis progression[10]. Serum MMP-3 was closely related to knee joint symptoms in rheumatoid arthritis patients[11].

Initially, the role of MMP-3, as an important cartilage-degrading enzyme in knee osteoarthritis (KOA), was suggested in a rat model[12]. Recent studies found out that this enzyme played an important role in the

pathogenesis of osteoarthritis (OA)[13,14]. Finally, if we consider the level of genetics, MMP3 polymorphisms may predict the activity and severity of OA[15].

MMP-3 levels in moderate and advanced OA are higher than those in early OA and healthy controls[14]. In addition, MMP-3 levels correlate with the reduction in the volume of the hyaline cartilage over time[16] and polyarticular involvement[17]. Although serum MMP-3 concentration was also shown to predict radiographic narrowing of the joint space[18], to our knowledge, its prognostic ability was not evaluated by a more sensitive imaging technique for reporting the progression of cartilage damage in KOA such as magnetic resonance imaging (MRI). Since semi-quantitative assessment of the joints by expert interpreters of MRI data has increased our understanding of the natural history of this complex disease, current Osteoarthritis Research Society International (OARSI) recommendations advocate the use of MRI for assessing cartilage morphometry in trials of OA[19].

Therefore, we aimed to explore the predictive value of baseline serum MMP-3 levels for the subsequent progression of cartilage damage in the medial tibiofemoral compartment of the knee joint in patients with KOA while controlling for the effects of other potential predictors in the model.

MATERIALS AND METHODS

DESIGN

One-year observational prospective clinical study

PATIENTS

Fifty-six patients, including 6 males and 50 females, aged 40 to 80 years (62.59 ± 10.11 years) who met the American College of Rheumatology (ACR) criteria for KOA[20], were included in this prospective, longitudinal, observational clinical study from 2015 to 2017. Briefly, all the participating patients suffered from symptomatic unilateral or bilateral KOA engaging the medial tibiofemoral joint space with a duration of complaints of more than 6 months. Patients who met one or more of the exclusion criteria in Table I were not included in the study. All patients provided written informed consent prior to clinical, serological, and imaging assessments at the baseline visit. The study was approved by the local Medical Ethics Committee.

After clinical examination, laboratory and imaging tests were completed at the baseline visit, and treatment was initiated in line with the local guidelines for the treatment of KOA.

MMP-3 LEVELS MEASUREMENT

Serum levels of matrix metalloproteinase 3 were measured during the baseline visit, as a potential prognostic biomarker. For this purpose, an enzyme-linked immunosorbent assay (ELISA) kit (BMS2014/2, Affymetrix, eBioscience, BenderMed Systems GmbH, Austria) was used, whereas the "biologic detection limit" (calculated as 2.0 SD above the analytic detection limit) is 0.008 ng/mL. The ELISA plates were read at 450/630 wavelength. Serum MMP-3 concentrations were determined using a standard curve according to the manufacturer's instructions in nanograms per milliliter (ng/ml). The assays were performed blindly, without prior knowledge of the patient's clinical and imaging characteristics. Serum MMP-3 measurement was performed at the same time for all samples.

Serum samples were collected by standard venipuncture with vacuum tubes from overnight-fasted knee OA patients who were asked to rest at least 30 minutes before blood collection.

IMAGE OBTAINMENT AND INTERPRETATION

Plain radiography. Anteroposterior radiographs of both fully extended knees were carried out at baseline and at the end of the follow-up. For this purpose, a digital X-ray machine "GE Precision Rxi" was used. Patients were asked to stand in an upright weight-bearing position while being radiographed. The images were interpreted by a specialist in imaging diagnostics who stratified the patients according to the Kellgren-Lawrence system into three groups (KLI, KLII, KLIII)[21].

Magnetic resonance imaging. The magnetic resonance images were obtained in the imaging department with magnetic resonance "GE Signa HDxt" with 1.5 T field intensity. MRI scans were carried out at baseline and the end of the follow-up on the symptomatic knee in patients with unilateral KOA, and in case of bilateral involvement - on the knee, which showed more advanced structural damage, according to the Kellgren-Lawrence scale. The scanned knee was called the "index" knee. If both knees showed the same grade of radiographic progression, the index knee was chosen based on the patient's perception of the more painful joint.

Images were evaluated according to the Whole-Organ magnetic Resonance iMaging Score (WORMS) by

TABLE I. EXCLUSION CRITERIA FOR THE STUDY

Exclusion Criteria	Explanation
End-stage KOA	IV KL radiographic stage
Comorbidities	Rheumatic diseases: rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, vasculitis and systemic connective tissue diseases, fibromyalgia; decompensated metabolic or cardiovascular disease
Traumatic event	Pre-existing intra-articular fracture or documented high-energy trauma of the lower limb
OA treatment	Systemic glucocorticoids (doses > 7.5 mg) and intra-articular hyaluronan, glucocorticoids or orthobiotics (e.g. platelet rich plasma) 3 and 6 months prior baseline visit, respectively; treatment with symptomatic slow acting drugs for OA (glucosamine, chondroitin, Avocado/Soybean Unsaponifiables) 6 months prior baseline visit
Deformity of the lower limb	Valgus or varus deformity of the knee joints > 20 degrees

KL – Kellgren-Lawrence; KOA – knee osteoarthritis; PRP – platelet-rich plasma; OA – osteoarthritis.

at least one independent imaging specialist. WORMS is a system for semi-quantitative evaluation of the magnetic resonance characteristics of KOA, namely: loss of hyaline cartilage, subchondral bone marrow lesions, subchondral cysts, osteophytosis, bone erosions, meniscal injury, and synovitis or synovial effusion, as well as damage of the oblique ligaments[22]. WORMS uses a complex sub-regional division of knee areas. The WORMS method provides a multifunctional full knee assessment for KOA using conventional magnetic resonance images, shows a high degree of agreement among trained assessors, and is validated in a longitudinal study[23,24].

In accordance with WORMS, the below definitions were used to interpret the MRI scans and to establish a structural change in tibiofemoral cartilage during the follow-up. Cartilage damage at baseline was present if a focal partial- or full-thickness loss of the cartilage of less than 1 cm in its greatest width was observed or there were areas of diffuse partial or total cartilage loss (WORMS score ≥ 2). If worsening in the WORMS score (WORMS ≥ 1), reflecting the cartilage injury in the medial tibiofemoral region, was observed after 12 months in the same patient, progression of cartilage damage was registered. These patients were indicated as progressors, while patients with no change or improvement in the cartilage of the medial tibiofemoral compartment were designated as non-progressors.

STATISTICS

The statistical analysis was performed using the SPSS 21 software product. The distribution of the data was calculated by the Shapiro-Wilk test. Descriptive statistics and non-parametric tests were used. Spearman rank analysis was carried out to investigate correlations between variables with non-normal distribution. Fisher's exact test was used to analyze the presence of a linear relationship between categories. Non-normally distributed variables were compared with the Mann–Whitney U-test. Binary logistic regression has identified the relationship between possible predictors (age, BMI, gender, generalized OA, therapy) and predicted variable (progression of cartilage damage in the medial tibiofemoral compartment). A Cochran-Mantel-Haenszel test was used to assess the conditional independence of categorical predictors associated with categorical outcomes. A receiver operating characteristic (ROC) analysis was conducted to establish the threshold values separating progressors from non-progressors. The area under the curve (AUC) was also calculated, as diagnostic tests approaching 1.0 indicated perfect discrimination between groups. The sensitivity and specificity of the proposed cut-off points for MMP-3 were also measured.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Complete baseline and follow-up data were collected from 50 out of 56 (89.2%) patients included in the study. Six patients were excluded from analysis due to lost to follow-up. Cartilage injury progression in the medial tibiofemoral compartment was seen in 13 (26%) participants with KOA. Relevant demographic and clinical features of KOA patients with and without

advancement of cartilage damage in the medial tibiofemoral compartment are presented in Table II. Expectedly, progressors have statistically higher body mass index (BMI) than non-progressors (30.1 [27.6; 37.2] vs. 27,6 [23.3; 38.8], p = 0.011). Significantly higher levels of MMP-3 were observed in patients with a progression of cartilage injury in the medial compartment of the knee (44.3 [26.1, 128.2]) than in patients with no progression (30.7 [12.6; 82.5]) on the 12th month (Mann-Whitney U = 114.5, p = 0.005).

FOLLOW-UP AND TREATMENT

One-year change in pain and disease severity of the study population, together with treatment during follow-up, are shown in Table III dichotomized by the presence and lack of progression in the medial tibiofemoral compartment of the knee joint.

PREDICTIVE VALUE OF BASELINE SERUM MMP-3

Binary logistic regression analysis showed that each increase in MMP-3 with 1 ng/ml increases the chance of progression of cartilage damage in the medial tibiofemoral compartment by approximately 4% (OR = 1.042, CI 95%: 1.002-1.084, p = 0.04). Potential confounders (age groups, sex, BMI, therapy, generalized OA) did not influence the outcome after conducting the Mantel-Haenszel test and the partial correlation coefficient.

In order to delineate progressors from non-progressors by means of the ROC analysis, we used baseline MMP-3 levels (Figure 1). The area under the curve (AUC) for serum MMP-3 levels was 0.761 (95%CI, 0.614-0.910), suggesting a good predictive accuracy of this biochemical test. The ROC curve set high cut-off levels (40.8 ng/ml) with a sensitivity of 69.2% and a specificity of 70.3% for differentiation between progressors and non-progressors. 100% specificity for distiguishing non-progressors from progressors was achieved at biomarker levels below 26.1 ng/ml with a sensitivity of 32.4%.

DISCUSSION

It has already been suggested that higher serum levels

TABLE II. BASELINE DEMOGRAPHIC, CLINICAL, AND IMAGING FEATURES OF PATIENTS WITH PROGRESSION (PROGRESSORS) AND LACK OF PROGRESSION (NON-PROGRESSORS) IN THE MEDIAL TIBIOFEMORAL COMPARTMENT OF THE KNEE JOINT

Variables	Patients with progression N = 13	Patients with no progression N = 37	p-value
Demographics			
Age (years)	64 (51; 80)	60 (40; 79)	NS
BMI	30.1 (27.6; 37.2)	27,6 (23.3; 38.8)	0.011
Female (%)	92.3%	84.3%	NS
Clinical characteristics			
Pain duration (years)	3.5 (0.5; 17)	5 (0.5; 13)	NS
VAS (pain, mm)	48 (24; 75)	54 (22; 95)	NS
Lequesne algofunctional index (disease severity)	10.5 (6; 23)	12 (4; 22)	NS
Imaging characteristics			
KLI	6	10	NS
KLII	6	17	
KLIII	2	9	
WORMS MFTJ cartilage morphology score	16.5 (4; 24)	15 (5; 27)	NS
MMP-3 values			
MMP-3 (ng/ml)	44.3 (26.1, 128.2)	30.7 (12.6; 82.5)	0.005

BMI = Body Mass Index; GlS = glucosamine sulfate; MMP-3 = matrix metalloproteinase-3; MFTJ = medial femorotibial joint; KL = Kellgren-Lawrence; NS = not significant; PRP = platelet rich plasma; VAS = visual analogue scale; WORMS = Whole-Organ Magnetic Resonance Imaging Score. The presented data are non-normally distributed and presented as median (min; max)

TABLE III. ONE-YEAR CHANGE IN PAIN AND DISEASE SEVERITY AND TREATMENT DATA OF PATIENTS WITH PROGRESSION AND LACK OF PROGRESSION IN THE MEDIAL TIBIOFEMORAL COMPARTMENT OF THE KNEE JOINT

Variables	Patients with progression N = 13	Patients with no progression N = 37	P
Change in clinical characteristics			
Change in VAS (pain, mm)	-10 (-42; 12)	-3 (-14; 9)	0.014
Change in Lequesne score	-1.5 (-5; 4.5)	0 (-3.5; 2)	NS
Treatment			
Oral GlS	5	8	NS
Intraarticular hyaluronan	7	24	
Intraarticular PRP	1	5	

GlS = glucosamine sulfate; NS = not significant; VAS = visual analogue scale.
The presented data are non-normally distributed and presented as median (min; max)

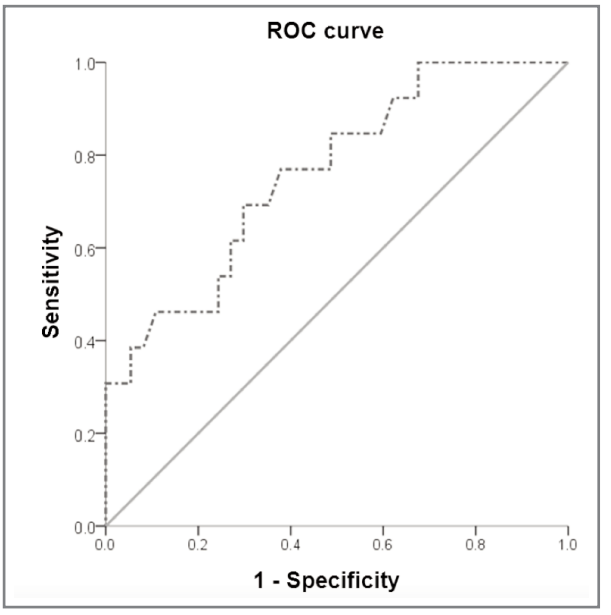

FIGURE 1. ROC curve differentiating progressors from non-progressors using serum MMP-3 (AUC = 0.761)
ROC: receiver operating characteristics; MMP-3: matrix metalloproteinase-3; AUC: area under the curve.

of MMP-3 and other serum markers are associated with advanced structural changes in patients with KOA and polyarticular involvement of OA[2,17,25]. One step further would be to understand whether synovial biomarkers and in particular MMP-3, can carry potentially important information for the prediction of future cartilage injury in OA patients. Logically, higher levels of endopeptidases would pose a greater risk to more intensive degradation of extracellular matrix components and, as is the case with MMP-3, activation of other molecules from the matrix metalloproteinase family[6,7] which provides a sound theoretical basis for investigation in this direction. The one-year follow-up period with imaging modalities was in line with the current recommendations of OARSI for determining the minimum time interval for detection and accurate assessment of structural changes by X-ray and MRI[19]. The medial tibiofemoral compartment is the most commonly affected by OA and more sensitive to change over time in comparison to the other two compartments of the knee joint[26].

In the study group, MMP-3 levels were associated and were an independent predictor for the progression of structural damage. Any increase in MMP-3 by 1 ng/ml elevated the likelihood of cartilage damage deterioration by 4%. These results did not depend on BMI, treatment or polyarticular involvement. Based on these data, a ROC curve was constructed which set a value of 40.8 ng/ml as the boundary between the progressors and the non-progressors. Therefore, the predictive value of serum MMP-3 levels for subsequent structural changes suggests that MMP-3 alone or in combination with other prognostic biomarkers may be used as a surrogate indicator for KOA patients with more rapid progression of cartilage damage. Theoretically, patients with higher levels of MMP-3 should be treated more aggressively in the early stages of the disease in order to conserve cartilage.

As far as we know, to date, this is the first prospective observational study that establishes a relationship between MMP-3 levels and the subsequent magnetic resonance progression of cartilage injury in patients

with KOA. Nevertheless, an association between structural damage and serum MMP-3 levels was established in 2005 when Lohmander *et al.* reported that MMP-3 serum concentration could predict radiographic narrowing of the joint space observed over a period of 30 months in patients with KOA[18]. Such a finding was not observed in the present study probably due to the short follow-up period and the small sample size. Serum MMP-3 was also associated with the progression of radiographic damage in inflammatory joint diseases such as ankylosing spondylitis, early and advanced rheumatoid arthritis[11,27,28].

Limitations of this study include low sample size and a relatively short follow-up period for registering structural progression in OA. We assume that only 13 patients were classified as progressors, which may represent the main limitation of the work. Since neither any data about the size of a "relevant effect" beforehand were available, nor were much knowledge about the expected variance, our research pretends to be exploratory. It raises the prospect that simple blood tests may be available to predict the progression of the disease course in patients with KOA. Measuring the levels of serum MMP-3 may be even implemented in clinical practice if confirmed in further studies. It may provide additional information to clinicians when making treatment decisions, since osteoarthritic patients with high cartilage turnover may show increased responsiveness to therapy with cartilage protecting effects[29,30]. Because our study was limited to an assessment of the medial compartment of KOA and the lateral compartment was not assessed, our results might be somewhat weakened.

CONCLUSION

In conclusion, serum MMP-3 levels may serve as a potential prognostic biomarker for cartilage injury in patients with KOA, identifying those at higher risk of disease progression. Further investigations in larger cohorts are warranted before any firm conclusions are made.

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