ORIGINAL RESEARCH PAPER

Rheumatology

SERUM MMP-7 LEVELS AS A PREDICTOR OF KNEE OSTEOARTHRITIS SEVERITY

KEY WORDS: Osteoarthritis, MMP-7, Kellgren-Lawrence Grading Scale

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ABSTRACT

This objective of this study was to evaluate the accuracy of MMP-7 in predicting severe degree of osteoarthritis (OA). A cross-sectional study was done on 55 consecutive knee OA patients that were admitted to Rheumatology division at Adam Malik General Hospital Medan, Indonesia. Disease severity in the knee OA patients was assessed using the Kellgren–Lawrence (K–L) grading scale. Serum MMP-7 levels were examined in serum using the Quantikine Human MMP-7-ELISA. Serum MMP-7 levels were significantly higher in moderate + severe knee OA than mild knee OA patients. MMP-7 was able to predict the severity of OA. Levels of MMP-7 > 12.65 pg/mL were able to predict moderate + severe OA with 66.7% sensitivity and 68.2% specificity.

Introduction

Osteoarthritis (OA) is a debilitating disease in the joints especially load-bearing areas such as knees. 1 It is a degenerative disease characterized by changes in chondrocytes and degradation of cartilage extracellular matrix (ECM).2 Progression of OA due to ECM composition and structure changes. Synovium inflammation during OA affects chondrocytes that are responsible for ECM turnover. Persistent inflammation in OA will directly induce catabolic activities of chondrocytes.[3,4]

In the OA occurs ECM destruction by inflammatory cytokines secreted by cartilage cells that cause joint inflammation and cartilage cell destruction. If ECM production such as type 2 collagen, proteoglycan, and aggrecan decreases, and ECM decomposition is activated by matrix metalloproteinases (MMPs) due to cartilage cell destruction, then the cartilage structure will be damaged, thus the patient may experience OA. [5]

Matrix metalloproteinases are a family of zinc-dependent endopeptidases collectively capable of degrading all components of the extracellular matrix. The MMPs consists of 28 members, and all amino acid sequences of MMPs have 2 domains, catalytic and prodomain domains, which are important as substrates, including gelatinases, collagenases, matrilysins, stromelysins, membrane-type MMP, and metalloelastases.6 MMP-7, also known as matrilysin, pump-1 protease, or uterine metalloproteinase is a member of the MMPs family consisting of structural related zinc-dependent endopeptidases. MMP-7 is the smallest member that only consists of the common catalytic domain and zinc-binding region.7 The role of MMP7 is to break down extracellular matrix by degrading macromolecules including casein, type I, II, IV, and V gelatins, fibronectin, and proteoglycan.[8]

MMP-7 is a potential biomarker involved in the pathogenesis of OA. The role of MMP-7 in OA had been widely studied.9-11 Studies that investigated the ability of MMP-7 in predicting the severity of OA were still limited. The objective of this study was to evaluate the accuracy of MMP-7 in predicting severe degree of OA.

Methods

Patient Selection

A cross-sectional study was done on 55 consecutive knee OA patients that were admitted to Rheumatology division at Adam Malik General Hospital Medan, Indonesia from October 2017 and March 2018. Subjects with other etiologies of knee joint diseases (such as rheumatoid arthritis, gouty arthritis, septic arthritis, post traumatic or dysplasias), evidence of malignancy, metabolic disorders, and systemic diseases were excluded. All patients gave informed consent and the study was approved by the Institutional Review Board of Universitas Sumatera Utara.

Diagnosis of knee OA

The diagnosis of knee patient with OA was confirmed by clinical examination and radiographic, which also fulfilled the criteria of the American College of Rheumatology (1987). Radiographic severity was assessed according to the Kellgren-Lawrence (K-L) grading system: grade 1, doubtful narrowing of joint space and possible osteophytic lipping; grade 2, definite osteophytes and possible narrowing of joint space; grade 3, moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour; grade 4, large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour. 12 OA were classified into mild (K-L grade 2), moderate (K-L grade 3), severe (K-L grade 4). Only patients with radiographic OA, defined as KL score of ≥2, were included in the study.

Serum levels of MMP-7

Venous blood was drawn using a serum separator tube and allowed to clot for 30-45 minutes at room temperature before centrifugation for 15 minutes at approximately 1,000g. Serum was immediately stored frozen in aliquots at -20oC until assays for MMP-7 were performed. Circulating MMP-7 levels were examined in serum using the Quantikine Human MMP-7-ELISA (Quantikine, R&D System, Inc., Minneapolis). Serum levels were expressed as pg/mL.

Statistical analysis

The data were analysed using independent t-test and ROC curve with 95% confidence intervals. A p-value < 0.05 was considered statistically significant. SPSS version 22 (SPSS Inc., Chicago) was used for analysis.

Results

A total of 24 patients with mild knee OA, and 31 patients with moderate + severe knee OA. There were no significant differences in age, sex, and BMI between patients with mild knee OA and moderate + severe OA (p>0.05).

Table 1. Baseline characteristics in knee OA patients

Variable	Mild knee OA n=24	Moderate+severe OA n=31	p
Age (years)	56 + 3.76	59 + 4.98	0.628
Gender Female Male	12 (40%) 12 (48%)	18 (60%) 13 (52%)	0.551
Body mass index	26.5 + 3.7	27 + 4.1	0.384

There were significant differences in serum MMP-7 levels between mild knee OA and moderate + severe knee OA (p=0.006). Serum MMP-7 levels were significantly higher in moderate + severe knee OA than mild knee OA patients (Table 2 and Figure 1).

Table 2. Comparison of serum levels of MMP-7 in mild knee OA and moderate + severe knee OA

	Mild Knee OA	Moderate+Severe Knee OA	p
MMP-7 (pg/mL)	12.61 + 2.62	15.17 + 4.57	0.006*

*p<0.05

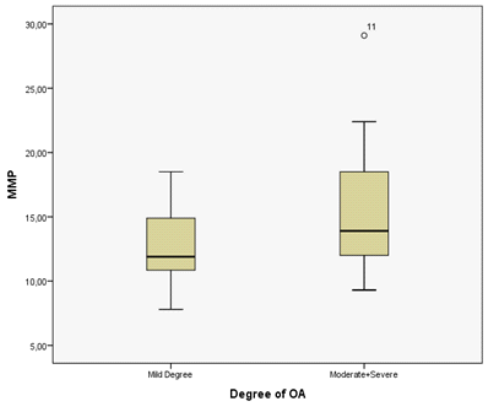

Figure 1. Serum levels of MMP-7 in mild and moderate + severe knee OA

MMP-7 was able to predict the severity of OA with p = 0.010 as shown in Figure 2. Levels of MMP-7 > 12.65 pg/mL were able to predict moderate + severe OA with 66.7% sensitivity, 68.2% specificity, 61.1% positive predictive value (PPV), 73.2% negative predictive value (NPV), 2.1 positive likelihood ratio (PLR), 0.49 negative likelihood ratio (NLR), and 67.5% accuracy (Table 3).

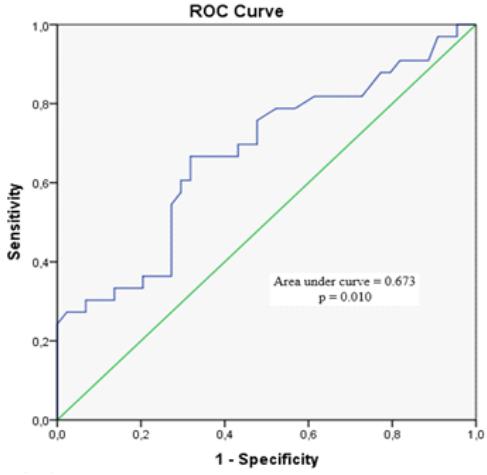

Figure 2. ROC curve of MMP-7 levels to predict the degree of OA (p = 0.010; area under curve = 0.673)

Table 3. Accuracy of MMP-7 levels to predict moderate + severe OA

Cut off	Sensitivity	Specificity	PPV	NPV	PLR	NLR	Accuracy
>12.65 pg/mL	66.7%	68.2%	61.1 %	73.2 %	2.1	0.49	67.5%

Discussion

Imaging is a modality to determine the severity and/ or progression of structural changes in OA patients. Currently, many biomarkers were examined from blood and synovium to predict the severity of OA. 13-18 One of the interesting markers to investigate was the MMP.

The biological roles of the MMPs have been traditionally associated with the degradation and turnover of most of the components of the ECM. The MMPs play an important role in tissue remodeling associated with various physiological or pathological processes such as morphogenesis, angiogenesis, tissue repair, cirrhosis, arthritis, and metastasis. [19,20]

MMPs are a family of zinc endopeptidases that cleave nearly all components of the extracellular matrix including collagens, elastin, matrix glycoproteins and proteoglycans and are thought to be responsible for the degeneration of articular cartilage.21 Previous studies had reported that there were an increased of MMP-7 levels in OA patients. 9,22 High levels of MMP-7 enhanced plasmin activation to render extracellular matrix vulnerable to degeneration and injury.[23]

This study found that serum MMP-7 levels were significantly higher in moderate + severe knee OA than mild knee OA patients. MMPs were believed to be involved in the progression of OA. 24,25 High protein levels of MMPs in OA might accelerate the pathogenesis of the disease. 11 Our results indicated that MMP-7 can be a potential biomarker to predict the severity of knee OA. Levels of MMP-7 > 12.65 pg/mL were able to predict moderate + severe OA with 66.7% sensitivity and 68.2% specificity. It is necessary to examine the accuracy of MMP-7 expressions of synovium to predict the degree of OA and the role of other MMPs.

Conclusion

Serum MMP-7 levels were significantly higher in moderate + severe knee OA than mild knee OA patients. MMP-7 was able to predict the severity of OA. Levels of MMP-7 > 12.65 pg/mL were able to predict moderate + severe OA with 66.7% sensitivity and 68.2% specificity.

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