ORIGINAL ARTICLE

Cartilage Oligomeric Matric Protein (COMP) Serum as a Biomarker for Early Diagnosis and Severity of Knee Osteoarthritis: A study on Elderly at UIN Research Teaching Clinical Unit (RCTU) in Banten, Indonesia

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ABSTRACT

Introduction: Osteoarthritis (OA) is a chronic degenerative disease caused by degeneration of cartilage in the joints. Radiological images based on Kellgren-Lawrence (KL) classification can be used for diagnosis and severity of knee OA. However, this assessment is not sensitive regarding inter-observer reliability. Various attempts have been made to find markers of cartilage damage. One potential marker is Cartilage Oligomeric Matrix Protein (COMP) serum. Based on animal studies, the more severity damage of joint cartilage, the more COMP serum is released. Thus, this study want to know the association between COMP serum with severity of knee OA based on KL. **Method:** This study is a cross sectional analytic study with secondary data whose performed with 147 subjects at UIN Research Teaching Clinical Unit (RCTU) in Banten, Indonesia. The diagnosis severity of knee OA based on KL. COMP serum subjects are checked by using ELISA method. The association between COMP serum with severity of knee OA was analyzed by Kruskall Wallis test. **Result:** Subjects the age group 70-79 years old had a COMP serum higher (790 ng/dl) than subjects the age group 60-69 years old (665,5ng/dl). The highest of COMP serum was found at grade 3 severity OA based on KL (783 ng/dl). **Conclusion:** There was no statistically significant association found (p=0.074) between COMP serum and the severity of knee OA on elderly.

Keywords: COMP serum, Knee osteoarthritis, Kellgren-Lawrence classification, Elderly

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INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disease caused by degeneration of cartilage the joints that increased friction between bones (1). Basic health survey in 2018 reveals the prevalence joint disease in Indonesia was 7.3%. The most impressive increase seen within the age group 35-44 years old (2).

Diagnosis of knee OA can usually be made by history and physical examination including signs and symptoms of knee pain with stiffness, joint crepitus and functional limitations, typically in a population above 50 years old. Diagnosis is confirmed by radiographs demonstrating changes such as osteophytes and joint space narrowing, subchondral bone sclerosis and cysts, and graded according to Kellgren- Lawrence (3).

Radiological images OA is not objective enough because it relies on experience and expertise of the radiologist, thus allowing inter-observer bias. Diagnosis OA also often at an advanced stage, because conventional radiographs to detect joint damage at an early stage is limited. It has an implications for higher failures to prevent disability. Thus, biomarkers of joint cartilage damage are needed to assess the severity of OA earlier and objectively. During the process of cartilage matrix turnover, cartilage matrix fragments and various macromolecules are released into the synovial fluid and the blood (4).

Cartilage Oligomeric Matrix Protein (COMP) is a thrombospondin- like structure. It is being considered as extracellular matrix stability (5-7). In animals, COMP was expressed in the earliest phase and increased further in more severe OA (7-8). According to the results of a study by Clark (1999) on the Caucasian race, COMP can reflect the severity OA (9). Fatimah recommend COMP serum more sensitives (96,30%) than CTX-II (59,26%) (10). Singh study COMP serum can be used to diagnose

normal and diseased individual and also asses different grade of severity of OA(11). The use COMP serum as a biomarker for early diagnostic will be useful in assessing severity of OA. especially knee OA. Thus, this study want to know the association between COMP serum with severity of knee OA based on KL.

MATERIALS AND METHODS

This study used a cross-sectional analytic method with secondary data and has been approved by Research Ethics and Community Service Commission, Faculty of Public Health, University of Indonesia. The subjects were invited to the study in January 2017, given inform consent and recruited from UIN Research Teaching Clinical Unit (RCTU). All recruited subjects over 60 years old, BMI below 27 kg/m2, with symptomatic OA, without prior heavy physical activity the previous month, history of knee trauma, other systemic inflammation diseases, undergone arthroplasty, arthrodesis and osteotomy subsequently undergone physical examination, COMP serum measurement and knee radiologic examination. 147 subjects agreed to join the study and completed all examinations.

Blood samples collected from all subjects for COMP serum measurement using ELISA method in a certified clinical laboratory (Prodia). Radiologic examination conducted at Sari Asih Hospital and interpreted by an orthopedist and classified based on KL (Grade 0: signifying no presence of OA, Grade 1: Doubtful narrowing of the joint space and possible osteophytic lipping, Grade 2: Definite osteophytes and possible narrowing of the joint space, Grade 3: Moderate multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends, Grade 4: Large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends).

Data checked for normality and was being analyzed by Kruskall Wallis test. Proposed COMP serum cut of point by Singh et al. Normal (up to 652.5 ng/mL), Grade 1 (up to 801.5 ng/mL), Grade 2 (up to 1100.5 ng/mL) and Grade 3 (over 1100.5 ng/mL) used to against our KL grading and COMP serum data. Based on central agency for elderly statistics in Indonesia, old age is categorized into the age group 60-69 years old and the age group 70-79 years old. Based on DEPKES Indonesia 2003. Body Mass Index (BMI) is categorized into very underweight (BMI <17 Kg/m^2), underweight (BMI 17-18.4 Kg/m^2), Normal (BMI 18.5-25 Kg/m^2), and obese (BMI 25.1-27.0 Kg/m^2).

RESULTS

This study revealed that majority subjects was female (72.8%) and most of subjects were included in the age group 60-69 years old (73.5%) with BMI in the normal category (87%). The highest median COMP serum was found at grade 3 severity OA (783 ng/dl) and the lowest at grade 1 severity OA (685.8 ng/dl) during the time of this study (Table I). There was no statistically significant association (p=0.074) between COMP serum and the severity OA (Table II). The highest median COMP serum was 800 ng/ml on the age group 70-79 years with grade 2 severity OA and there was no statistically significant association between COMP serum and age (p=0.163) (Table III).

Table I: Basic characteristics of subject

Variable	count (n)	Per-centage (%)	COMP ng/mL			P value
			mean	median	Min-Max	
Sex						
Male	40	27.2	772.1	729	355-1870	0.010
Female	107	72.8	733.6	680	358-2160	0.000
Age						
60-69 years old	108	73.5	698.6	665.5	355-2160	0.001
70-79 years old	39	26.5	867.5	790	359-1870	0.027
BMI						
<17 Kg/m^2	2	1.4	768.5	768.5	639-898	0.200
-18.4 Kg/m^2	7	4.6	775.8	661	369-1559	0.010
18.5-25 Kg/m^2	87	59.2	730,7	680	355-2160	0.003
25.1-27 Kg/m^2	51	34.7	769.5	711	378-1870	
Severity of OA based on *Kellgren Lawrence* classification						
Grade 1	63	42.9	685.8	685.8	355-2160	0.000
Grade 2	58	39.5	778.8	699	358-1613	0.000
Grade 3	26	17.7	862	783	465-1870	0.200
COMP serum	147	100	746.8	685	355-2160	0.000

Table II: Association between COMP Serum Concentration and the severity of osteoarthritisbased on Kellgren Lawrence classification

Severity of OA based on Grade	Median (Min-Max)	Count (n)	P value
1	613(355-2160)	63	0.074*
2	699(358-1613)	58	
3	783(465-1870)	26	

DISCUSSION

COMP is an extracellular matrix glycoprotein member of the thrombospondin family of calcium binding proteins. It has been shown to influence the fibril formation of collagens I and II by promoting early association of collagen molecules thereby accelerating fibrillogenesis with a distinct organization of the fibrils. COMP is not synthesized only by cartilage, but also by synovial cells and osteoblasts. It is released in response to damage in cartilage (5). In knee OA, gender is one of risk factor for OA, female around the time of menopouse more likely have a risk of OA because estrogen factors may play role in the development of OA. Based on age, incidence of OA occur with aging that make a joint

Table III: Association between COMP Serum Concentration on gender, age, and BMI based on the severity of osteoarthritis according to Kellgren Lawrence classification

Variable	OA severity						P value
	Grade 1		Grade 2		Grade 3		
	median (Min-Max)	count(n)	median (Min-Max)	count(n)	median (Min-Max)	count(n)	
Sex							
Man	630(355-1069)	17	647(358-10887)	15	868(541-1177)	8	0.002
Woman	611(359-2160)	46	705(420-1613)	43	696(465-1870)	18	
Age							
60-69 years old	597(355-2160)	55	680(358-1613)	45	696(586-1085)	8	0.163
70-79 years old	775(369-1431)	8	800(459-1382)	14	795(465-1870)	17	
BMI							
<17	898(898-898)	1			639(639-639)	1	0.325
17-18.4	661(369-1559)	5	644(459-829)	2			
-18.5-25	595(355-2160)	38	729(358-1382)	36	694(465-1191)	13	
-25.1-27	597(378-941)	19	686(420-1613)	20	947(567-1870)	12	

less able to cope with adversity such as weak muscle and cartilage thinning. Obesity as potent risk for OA, increased loading on the joint probably the main occur for OA (12). This study shows the more severity OA, the more COMP serum is released (Table I). However, there was no statistically significant association between COMP serum and the severity because the progression of OA was not linear (not continuous). Tseng proposed that OA is a disease progression. When OA is stable or not progressing, COMP serum will slowly return to near normal (5).

CONCLUSION

COMP serum is released in response to damage in cartilage and useful as a marker for OA presence. However, there was no statistically significant association between COMP serum and severity of OA based on KL.

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