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Cover image: (A) T1 weighted MRI of thoracic spine showed continuous OLF between T9-11; (B) T2 weighted MRI showed OLF (double dagger); (C) Canal stenosis on Axial T2 weighted image due to OLF (asterisk). See page 31 (see article **Myelopathy caused by Ossification of Thoracic Ligamentum Flavum**)

AIMS AND SCOPE

Indonesian Journal of Rheumatology is self-focused on rheumatic diseases and connective tissue disorders in forms of original article (extended or concise reports), review articles, editorial, letters, leaders, lesson from memorable cases, book review, and matters arising. Both clinical and laboratory including animal studies are welcome.

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Editor's note

YI Kasjmir

Indonesian Journal of Rheumatology come forward with a new attractive cover. With our new face, we will publish two times per year in order to satisfy your curiosity about novel researches and developments in rheumatology. We hoped cases and articles provided in the Journal may bring you new evidence-based informations and knowledges that could be used in your clinical practices.

In this edition, we would emphasize about SLE topic. We decided to publish three articles about SLE, two of them were about nephritis lupus. Nephritis lupus is known as the most common morbidity among SLE patients. It occurs majorly among SLE patients during the first 10 years of disease. About 25% of nephritis lupus would developed into end-stage renal disease within the first 10 years. Nephritis lupus can significantly reduce survival in SLE patients. Therefore diagnostic and severity index of nephritis lupus should be assessed immediatly in order to select the optimal treatment for each patients.

Gold standard for nephritis lupus is renal biopsy which is quite expensive and only available in tertiary centers. Facing the difficulty to diagnose, Enrica M, et al, original article suggested using anti-C1q serum test as diagnostic marker for lupus nephritis.¹ Unfortunately the test still have low sensitivity and medium spesifity. However, it still can be used for clinical surveilance test in SLE patients. The main symptom in nephritis lupus patients is proteinuria, resulted from glomerular filtration dysfunction and tubular reabsorption dysfunction. The gold standard to asses proteinuria is 24-hour protein urine collection. Eventhough quite simple assesment, but it may not convenience to collect urine for 24 hours. Aini YH, et al, original article, proposed random urine protein and creatinine (P-C) ratio could be an alternative for 24 hour proteinuria to asses quantitative index of proteinuria.² Eventhough, some study reported contradictory results because of daily variaton of protein in urine. Corrected constant creatinine excretion will eliminate the false results. The other importance examination in SLE patients is fatigue. Fatigue is the most common symptoms in SLE.

International Ad Hoc Committee has recommended the 'Fatigue severity scale' as instrument to validate fatigue condition in SLE. Unfortunately the test are not available in Bahasa Indonesia. Therefore, Rifa'i, et al, study assessed validity and reliability of fatigue severity scale within Bahasa Indonesia for assessing fatigue scale in SLE patients in Indonesia.³

In addition, this volume are also covered others important topics, such as correlation between OA grading in femoropatella joint and patellar malalignment using WOMAC score by Kiswati, et al,⁴ also an interesting article about efficacy and safety of Mahkota dewa fruit extracts compared to meloxicam for treating pain in OA patients by Rahmadi AR, et al,⁵ and an observational cross-sectional study about comorbidities in patients with Gout by Limanjaya WR, et al.⁶ And finally, do not forget to read the case report about a mylopathy caused by ossification of thoracic ligamentum flavum and the management, written by Yudoyono F, et al.⁷

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2. Aini YH, Tjandrawati A, Suraya N, Hamijoyo L. Correlation of random Urine Protein Creatinine (UPC) ratio with 24-hour Protein Urine in Lupus Nephritis Patients.
3. Rifa'i A, Kalim H, Kusworini, Wahono CS. Validity and reliability fatigue severity in patients with Systemic Lupus Erythematosus (SLE) in Indonesia.
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6. Limanjaya WR, Wachjudi RG, Tansah H. Comorbidities in patients with gout in rheumatology clinic Dr. Hasan Sadikin General Hospital in 2012-2013.
7. Yudoyono F, Dahlan RH, Ompusunggu SE, Hamijoyo L, Arifin MZ. Myelopathy caused by ossification of thoracic ligamentum flavum.

Validity and reliability fatigue severity scale in patients with Systemic Lupus Erythematosus (SLE) in Indonesia

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ABSTRACT

Background: Fatigue is one symptom of Systemic Lupus Erythematosus (SLE), which has an important effect on the quality of life. Fatigue Severity Scale (FSS) is one parameter fatigue symptom in SLE. The purpose of this study was to determine the validity and reliability between FSS with duration of illness and disease activity of SLE patients in Indonesia.

Methods: FSS performed on 40 patients with SLE. FSS original English version has been converted-translated into Indonesian version by a team of Rheumatology-Immunology Medical Faculty of Brawijaya University. Reliability determined by Cronbach's Alpha values (>0.6). Validity was determined by the value of Corrected Item-Total Correlation which each item was a valid question if below value of Cronbach's Alpha.

Results: The reliability value was determined by Cronbach's Alpha values (>0.6) in which the SLE patients in this study had a Cronbach's Alpha value of 0.946. Value of Corrected Item-Total Correlation overall under Cronbach's Alpha value (range = 0.684-0.859) which indicates that each item was a valid question. There were correlation between the FSS Indonesian version with disease duration ($p = 0.000$) as well as the value of $r = 0.581$, with SLEDAI ($p = 0.000$) with a value of $r = 0.833$.

Conclusion: FSS in Indonesian version has a good reliability and validity and can be used by clinicians and other researchers to assess the condition of fatigue in SLE patients in Indonesia.

Keywords: validity, reliability, fatigue, fatigue severity scale, systemic lupus erythematosus

Background

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease which has varied systemic clinical manifestations as well as the emergence of 'flare' or remission is difficult to predict.¹

Fatigue is one of the symptoms associated with inflammatory disease. It can be caused by many factors, among others, the degree of disease activity, medical therapy, or comorbid conditions such as depression and fibromyalgia.² Fatigue has a high prevalence in patients with SLE (67-90%) and may be the most dominant symptom, limiting daily activities of patients and the effect on patient compliance in the treatment process.^{2,3} Fatigue, though often experienced, quite difficult to measure because it is subjective and heterogeneous.

However, several methods have been made to measure/assess. An International Ad Hoc Committee has recommended the instrument can validate the condition of fatigue in patients with SLE, the Fatigue Severity Scale (FSS) in the original version in English.^{4,5} The FSS consists of nine items of questions about symptoms of fatigue, each item has a score ranging from one to seven. FSS has been translated into several languages,⁶⁻⁸ however to date, translation of the FSS into Indonesian has not been done. The purpose of this study was to determine the validity and reliability of Fatigue Severity Scale (FSS) in patients with SLE in Indonesia.

Methods

The study was conducted in the outpatient unit Rheumatology division of the Internal Medicine Department, RSSA Malang. FSS original English version has been converted-translated into Indonesian version by a team of Rheumatology-Immunology the Medical Faculty of the Brawijaya University.

Population and Sample Research

The population was affordable on the SLE patients who seek treatment in the Hospital Clinic of Internal Medicine Dr. Saiful Anwar. SLE diagnosis based on the 1997 ACR criteria. Sampling technique was consecutive sampling that all subjects who came and met the inclusion criteria based on a predetermined time. Inclusion and control subjects were women with SLE, aged 18-43 years, disease duration ≤ 1 year since SLE diagnosed, the disease was active with SLEDAI scores ≥ 5 . Subjects who signed informed consent had initial examination to diagnose, physical examination, determined SLEDAI score and FSS score. This study was approved by the Ethics Committee of the Medical Faculty of the Brawijaya University.

Statistical Analysis

Internal consistency reliability was tested by using Cronbach's alpha, where the value >0.7 means satisfactory, while the value of >0.9 can be used clinically.^{14,15} Validity was determined by the value of Corrected Item-Total Correlation where each item was a valid question if below value Cronbach's Alpha.⁹ Validity was tested by Spearman's rank correlation coefficient (r_s) to describe the

correlation between the FSS with disease duration and degree of disease activity (SLEDAI). rS values ≤ 0.25 is a little or no correlation, 0.26 to 0.49 showed weak correlation, 0.50-0.69 showed moderate correlation, 0.70-0.89 showed a strong correlation, and 0.90-1.0 showed a very strong correlation.⁹ Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences) version 17.0.

Results

The data of total 40 patients who participated in this study showed in Table 1.

Table 1 Characteristics of SLE Patients

Characteristics	Range	Mean (SD)
Age (years)	16-40	28.25 (6.97)
Disease Duration (month)	1-8	3.55 (1.90)
SLEDAI	7-23	12.65 (4.85)
FSS	3-7	5.41 (1.02)

The average age of SLE patients was 28.25 (SD 6.97) years (range 16 - 40 years old). The average of duration disease was 3.50 (SD 1.90) months. The average SLEDAI score of patient was 12.65 (SD 4.84), while the average of FSS score was 5.41 (SD 1.02).

Table 2 Translations FSS into Indonesian

English Version	Indonesian Version
My motivation is lower, when I am fatigued	Motivasi saya rendah sekali saat saya mengalami kelelahan
Exercise brings on my fatigue	Latihan fisik mengakibatkan saya mengalami kelelahan
I am easily fatigued	Saya mudah sekali mengalami kelelahan
Fatigue interferes with my physical functioning	Kelelahan mengganggu aktifitas fisik saya
Fatigue causes frequent problems for me	Kelelahan sering menjadi masalah saya
My fatigue prevents sustained physical functioning	Kelelahan menyebabkan saya tidak bisa bertahan lama dalam beraktifitas
Fatigue interferes with carrying out certain duties and responsibilities	Kelelahan mempengaruhi tugas dan tanggung jawab saya
Fatigue is among my 3 most disabling symptoms	Kelelahan merupakan salah satu dari 3 gejala utama yang membatasi aktifitas saya
Fatigue interferes with my work, family, or social life	Kelelahan mempengaruhi pekerjaan, keluarga atau kehidupan sosial saya

Reliability and validity of FSS

Reliability is determined by the value of Cronbach's Alpha values (>0.6) in which the SLE patients in this study had a Cronbach's Alpha = 0.946. As for the validity of the FSS can be seen in Table 3.

Table 3 Validity Fatigue Severity Scale (FSS)

Item question	Corrected Item-Total Correlation
Motivasi saya rendah sekali saat saya mengalami kelelahan	0.770
Latihan fisik mengakibatkan saya mengalami kelelahan	0.761
Saya mudah sekali mengalami kelelahan	0.831
Kelelahan mengganggu aktifitas fisik saya	0.715
Kelelahan sering menjadi masalah saya	0.859
Kelelahan menyebabkan saya tidak bisa bertahan lama dalam beraktifitas	0.842
Kelelahan mempengaruhi tugas dan tanggung jawab saya	0.794
Kelelahan merupakan salah satu dari 3 gejala utama yang membatasi aktifitas saya	0.684
Kelelahan mempengaruhi pekerjaan, keluarga atau kehidupan sosial saya	0.858

The Corrected Item-Total Correlation value overall were under Cronbach's Alpha value (range = 0.684-0.859) which indicated that each item was a valid question. This study showed the correlation between the FSS with duration of illness and disease activity (Table 4). There were relationship between the FSS and duration of illness because the value of $p < 0.05$ ($p = 0.000$) with $rS = 0.581$

Table 4 The correlation of FSS with duration of illness disease activity of LES patients

No	Variabel	P	r
1.	FSS with duration of illness	0.000	0.581
2.	FSS with disease activity	0.000	0.833

$P < 0.005$ significant relationship

There were also significant relationship between the FSS and disease activity (SLEDAI) because $p < 0.05$ ($p = 0.000$) with $rS = 0.833$

Discussion

This study reported that FSS-English version translated into Indonesian version and subsequently tested for validity and reliability in SLE patients whose disease onset < 1 year. Proven reliability with Cronbach's Alpha value. While the validity value also indicated that all items of FSS questions Indonesian version were valid.

Clinical features of SLE were varied, the European League Against Rheumatism (EULAR) recommended the use of quality of life assessment in clinical practice because the data was relevant or even overlooked.¹⁰ In this study FSS Indonesian version were valid to be used for clinical practice. Until now, fatigue evaluation performed by anamnesis/history of the patient, while the use of questionnaires have not been routinely performed in clinical practice.¹⁰ Assessment of patients, such as FSS can contribute to the evaluation of the SLE patient's health condition subsequent, both during daily clinical examination or for further treatment.

The validity and reliability in this study is consistent with the results of several previous studies. Reliability values respectively with Cronbach's alpha 0.89 on research conducted by Neuberger, 0.96 in the study by Lorentzen and 0.953 on Bakalidou study.^{11,9,12}

Besides, in this study it was found that a significant relationship between FSS and duration of illness and also with disease activity. Correlation with duration of illness has moderate power that means the longer duration of illness, the possibility of fatigue conditions in SLE patient were more severe. In disease activity, some research suggests that controversial results in terms on one side has a correlation but on the other hand does not exist.¹³⁻¹⁶ In this study, there were significant relationship with a positive correlation, but it occurs in patients with a limited population, patients with disease duration of less than 1 year. Although weak positive correlation was also reported in the study conducted by Lorentzen.⁹

Conclusion

This study indicated that Indonesian version of the FSS was valid and reliable method of measuring fatigue in patients with Systemic Lupus Erythematosus (SLE). It shows the role of the patient's clinical surveillance because it will give opportunity for SLE patient to measure and report the prevalence of symptoms that are important for quality of life.

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Correlation between osteoarthritis grading in femoropatella joint and patella malalignment with pain and disability using WOMAC score

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ABSTRACT

Background: Osteoarthritis (OA) in femoropatella often causes pain and disabilities in the lower extremities. In 2011 found a significance association between knee pain with osteophytes in femoropatella joints compared with osteophytes in femorotibia joints. Niu J et al. found knee joint with lateral patellar malalignment and lateral patellar tilt had increased prevalence of femoropatella OA, similar study in Caucasian and African Americans patients found an association between patellar malalignment with severe knee pain and disease progressivity. In this study, researchers correlate grading OA genu with pain and disability using WOMAC scores and malalignment correlate with pain and disability with WOMAC scores without assessing the progression of the disease. In this study, using cross-sectional at one time whereas previous studies using multi-center cohort were evaluated 3 to 5 years later to assess the progression of the disease.

Objective: to establish a correlation between OA grading in femoropatella joint and patellar malalignment with pain and disability using WOMAC Score.

Method: Observational analytic study with cross-sectional and consecutive sampling was performed in this study. In the WOMAC correlation with Kellgren-Lawrence grading on the WOMAC OA genu and grading narrowing between joints using the Rank Spearman while the different test WOMAC with malalignment using T test

Results: WOMAC OA genu of the grading (AP/LAT/Skyline) $r = 0.488$; $p = 0.003$, WOMAC OA genu of the grading (AP/LAT) $r = 0.452$; $p = 0.006$, WOMAC OA genu of the grading (AP/Skyline) $r = 0.362$; $p = 0.033$, WOMAC towards narrowing between joints grading femoropatella $r = 0.370$; $p = 0.026$, no differences between patellar malalignment with WOMAC score, with malalignment ($p = 0.711$) without malalignment ($p = 0.751$).

Conclusion: In AP/LAT/Skyline, AP/LAT, AP/Skyline position and grading narrowing femoropatella joint space was found a significant positive correlation between OA knee's grading and WOMAC score. No differences in T test between patella malalignment with pain and disability using WOMAC score.

Keywords: femoropatella osteoarthritis, patellar malalignment, WOMAC score.

Introduction

Osteoarthritis (OA) is a common disease in elderly. Knee joint has three compartment consist of lateral femorotibial, medial femorotibial and femoropatella compartment. Femoropatella joint is one of compartment knee joint that frequently affected by osteoarthritis.^{1,2}

Incidence of OA in femoropatella joint is higher than expected before, it is proven from several studies, Szebenyi B et al. investigated 334 patients with knee OA and found osteophyte in femoropatella in 218 patients and femorotibia in 184 patients.¹ Similarly, Duncan et al. investigated 774 patients with knee OA, found the combination of OA in femorotibia and femoropatella (4%), femoropatella OA (24%), and femorotibia (4%) and the remaining 32% were showed in normal radiograph ($p < 0.001$).¹

Osteoarthritis in femoropatella often causes pain and disability in lower extremities. It was proven by Crossley M Kay et al.² that found significant relationship of knee pain with osteophyte in femoropatella joint compare with osteophyte in femorotibia. This result was supported by Hunter et al.,⁵ showed that reduction of patella cartilage volume related to increment of pain and disability using WOMAC score. Similar study conducted by Cicuttini FM et al.³ showed that skyline projection was better in evaluating femoropatella OA better than lateral projection.

Knee OA classically was found, particularly in femorotibial joint thus radiograph evaluations tend to focus on AP projection, which cannot describe femoropatella joint. Classically views knee OA especially in femorotibia joint so that valuation radiography tend to focus only on the anteroposterior (AP) projection, which cannot describe femoropatella joint. If there was involvement of femoropatella joint in OA process, then it suggested to use lateral (LAT) and skyline projection. Skyline projection is effective to observe degenerative changing in femoropatella joint.³⁻⁷

Malalignment patella often describe as subluxation in femoropatella joint, it was related with narrowing of joint space and cartilage thickness. Niu J et al.⁵ study in Beijing found knee

joint with lateral patellar malalignment and lateral patella tilt was high then it concluded there was high prevalence OA in femoropatellar. Then similar study by Hunter D et al.⁵ which consist of Caucasian and America-African sample showed patellar malalignment related to severe knee pain and progression of disease.^{1,3,5,8}

Knee OA diagnostic criteria comprise of radiograph abnormality and clinical symptom. WOMAC score (*The Westerns Ontario and MacMaster Universities*) is used to evaluate pain and disability. While for pain only could be assessed by (*Visual Analogue Scale*) which is pain measurement that can be applied to various types of pain.⁹

STUDY METHOD

Study was conducted in Dr. Kariadi Hospital, Semarang. The sample were taken during February until October 2014. This study was observational analytic with cross-sectional method.

Research Sample

Patient clinically had pain in knee joint, and/or suspected as knee OA was examined in Internal Medicine station and was assessed by 3 position radiograph of knee in Diagnostic Radiology Unit of Dr. Kariadi Hospital Semarang, which fulfil criteria as follows.

Inclusion Criteria consists of age above 50 years old, they fulfil diagnostic criteria of knee joint OA clinically, and had been assessed by 3 position radiograph of knee (AP, LAT, Skyline). Exclusion criteria are they had been discovered other arthritis abnormalities apart of knee OA such as gout arthritis, rheumatoid arthritis or had been discovered fracture in tibia, fibula, or femoral bone.

Instrument and Study Procedure

Instrument

The instrument used was Radiograph plane of General Purpose GE Proteus XR type Siemens MX 100 machine with serial number 226173, 150 KV, 630 MA and Villa system medicali G100 RAD type RTM 782 with serial number 84K440, 150 KV, 630 MA. Work station of Master type View 4.5.3 with soft war Master View Dicom 4.5.3.

Study Procedure

This study used 3 projections (AP, LAT, Skyline). In AP position, patients conducted to stand upright without rotation and straight pelvic. Align and position the legs and genus right in the center line of the film. Directed the rays perpendicular lyto tibial at the center, which located 1 cm distal apex of patellar. The film distance focus was 100 cm, 56 kV, 5.6 mA/s. In lateral position, patient was conduct to standing with legs flexed 30 to 40 degrees. Skyline position or axial cuts describes relationship of distal patellar surface of femur (sulcus intercondylar or trochlear groove) and other distal part of the femur also be seen. At the skyline position with Lourine method, patient was conduct to sit on a table with legs flexed position forming an angle of 130 degrees and the film was held by patient, direct the rays of film at an angle of 90 degrees.

Data Analysis

The collected data was checked for its completeness and accuracy of data (data cleaning). Then the data was coded, tabulated and inputed into computer. Data analysis was consist of descriptive analysis with frequency table, graphic, dan mean (SD). Afterwards normality was tested from each variables as amount of samples >25 then Kolmogorov-Smirnov was used, and then using Pearson Correlation test if the data was normal. If the data was not normal, thus Rank Spearman was used. While nominal variable was used T-test.

STUDY RESULT

There were 36 samples that meet inclusion criteria, thus assessed with WOMAC score questionnaire and 3 positions radiograph of the knee (AP, LAT, and skyline).

General Characteristic of Study Subject

Study subjects' characteristics such as age, gender, occupation history, education history, BMI, and examination result of pain and disability obtained from the WOMAC score. The youngest age was 50 years old and the oldest was 76 years old with mean of age 60.58 years old. Most of respondents obtained in group of age 50-59 years old (47.22%). Most of study samples were women, 29 samples (80.56%), compared to men, 7 samples (19.4%). The lowest BMI was 17.58 and the highest was 41.65 with mean of BMI was 26.20. Most of BMI of knee OA patients were overweight patients around 63.9%, ideal body weight was 33.3%, and low body weight was 2.8%. Statistical test of demographic factor consist of age ($p = 0.402$), gender ($p = 0.397$), BMI ($p = 0.156$). In conclusion demographic factor does not affect the independent and dependent variables.

Table 1 Characteristics of study sample (n=36)

Characteristic	Mean (SD)	Median (min-max)	Frequency (%)	p Value
Age :	60.58 (SD 8.02)	24 (50 - 76)		0.402
≤ 50			2 (5.6)	
51-60			17 (47.2)	
61-70			15 (33.3)	
71-80			5 (13.9)	
Gender :				0.397
Man			7 (19.4)	
Woman			29 (80.56)	
BMI :	26.20 (SD 5.16)	17.58-41.65		0.156
Under weight			1 (2.8)	
Ideal weight			12 (33.3)	
Over weight			23 (63.9)	

Knee OA measurement

Lawrence-Kellgren knee OA grading

Of these, AP/LAT and skyline radiograph of the knee in 36 samples, all of radiographs showed combination of femorotibial OA and Femoropatellar OA. From 36 samples, about 31 samples had left and right radiograph of knee, meanwhile about 5 samples only had 1 radiograph of knee (right or left). Distribution of OA grading in femorotibia joint mostly in grade 2 around 25 subjects (37.3%), grade 3 in 25 subjects (37.3%),

grade 4 in 9 subjects (13.4%), and grade 1 in 8 subjects (12.05%). Distribution of OA grading in femoropatellar, mostly in grade 3 around 48 subjects (71.64%), grade 2 in 11 subjects (16.43%), grade 4 in 5 subjects (7.46%), and grade 1 in 3 subjects (4.47%). Based on data above which took the most severe degree of knee OA and showed the highest OA grading in this data was grade 3 around 24 subjects (66.7%), grade 4 in 7 subjects (19.4%), grade 2 in 4 subjects (11.1%), grade 1 in 1 subject (2.8%).

Table 2 Kellgren-Lawrence Grading of knee OA with AP/LAT/Sky line

Knee OA Grading	n (%)
Grade 1	1 (2.8)
Grade 2	4 (11.1)
Grade 3	24 (66.7)
Grade 4	7 (19.4)
Total	36 (100)

The author separated OA knee grading evaluation in Kellgren-Lawrence with AP/LAT examination and AP/Skyline. Distribution of knee OA with AP/LAT examination as follows: grade 3 in 15 subjects (41.67%), grade 2 in 11 subjects (30.56%), grade 4 in 6 subjects (16.67%), and grade 1 in 4 subjects (11.11 %).

Table 3 Kellgren-Lawrence Grading knee OA with AP/LAT

Knee OA grading	n (%)
Grade 1	4 (11.10)
Grade 2	11 (30.56)
Grade 3	15 (41.67)
Grade 4	6 (16.67)
Total	36 (100)

Whereas distribution OA knee with AP/skyline examination as follows: Grade 1 in 2 subjects (5.55%), grade 2 in 1 subject (2.78%), grade 3 in 28 subjects (77.78%) and grade 4 in 5 subjects (13.89%).

Table 4 Kellgren-Lawrence grading knee OA with AP/Skyline

Knee OA grading	N (%)
Grade 1	2 (5.55)
Grade 2	1 (2.78)
Grade 3	28 (77.78)
Grade 4	5 (13.89)
Total	36 (100)

Grading in narrowing of femoropatellar joint space

In skyline projection of grading in narrowing of femoropatellar joint space was evaluated, which consist of narrowing of medial side, lateral and central, patellar malalignment, angle sulcus and patellar tilt. Then grading of narrowing femoropatellar joint assessed the most severe one. From the examination result showed the most grading of joint space was grade 1

around 30 subjects (83.3%), no joint space narrowing (grade 0) in 4 subjects (11.1%), and grade 2 in 2 subjects (5.6%). There was no grade 3 of joint space narrowing in this study, as seen in Table 5.

Knee OA Based on Patellar Malalignment

This study showed that the lateral malalignment was found in 28 subjects (77.78 %), medial malalignment in 1 subject (2.78%) and no malalignment in 7 subjects (19.44%).

Table 5 Patellar Malalignment

Patellar Malalignment	n (%)
No Malalignment	7 (19.44)
Lateral Malalignment	28 (77.78)
Medial Malalignment	1 (2.78)
Total	36 (100)

Pain Measurement and Disability using WOMAC Score

In measurement of pain, stiffness, and disabilities using WOMAC score were obtained mild pain response value was 3 and severe pain value was 16, mild stiffness value was 1 and severe stiffness value was 6, while mild disability value was 9 and severe disability value was 49. The lowest of total WOMAC score was 13 and the highest score was 71 with mean 39.69 (SD 13.318).

Correlation test between WOMAC Score with Kellgren-Lawrence knee OA Grading with AP/LAT/Skyline projection

Based on Spearman's test between WOMAC score with Kellgren-Lawrence knee OA Grading with AP/LAT/Skyline projection showed significant positive correlation ($r = 0.488$; $p = 0.0003$).

Table 6 Correlation test of WOMAC with Kellgren Lawrence knee OA grading with AP/LAT/Skyline projection

Variable	WOMAC score	
	r	p Value
Kellgren-Lawrence knee OA Grading AP/LAT/Sky line	0.488	0.003

Significant correlation if p Value < 0.05

Correlation test between WOMAC Score with Kellgren Lawrence knee OA grading in AP/LAT Examination

Based on Spearman's test between WOMAC score with Kellgren-Lawrence grading of knee OA with AP/LAT projection showed significant positive correlation with moderate power ($r = 0.452$; $p = 0.0006$).

Table 7 Correlation test of WOMAC with Kellgren Lawrence knee OA grading with AP/LAT projection

Variable	WOMAC Score	
	r	p Value
Kellgren-Lawrence knee OA Grading AP/LAT	0.452	0.006

Significant correlation if p Value < 0.05

Correlation test between WOMAC Score with Kellgren-Lawrence knee OA Grading with AP/Skyline projection

Based on Spearman's test between WOMAC score with Kellgren-Lawrence grading of knee OA with AP/Skyline projection showed significant positive correlation with ($r = 0.362$; $p = 0.033$) weak power.

Table 8 Correlation test of WOMAC with Kellgren Lawrence knee OA grading with AP/Skyline projection

Variable	WOMAC Score	
	r	p Value
Kellgren Lawrence knee OA Grading AP/ Sky line	0.452	0.006

Significant correlation if p Value < 0.05

Correlation test between WOMAC score with grading in narrowing of femoropatellar joint space

Based on Spearman's test between WOMAC score with grading in narrowing of femoropatellar joint space showed significant positive correlation with ($r = 0.370$; $p = 0.026$) weak power.

Table 9 Correlation test of WOMAC with grading in narrowing of femoropatellar joint space

Variable	WOMAC score	
	r	p Value
Grading in Narrowing of Femoropatellar Joint Space	0.370	0.026

Significant correlation if p Value < 0.05

Differential Test (T test) between WOMAC score with patellar malalignment

Based on Kolmogorov-Smirnov test in WOMAC score and patellar malalignment showed that the distribution of sample was abnormal, and then t-test was conducted because patellar malalignment had a nominal scale. From the t test there is no difference of WOMAC score in patellar malalignment. After conducted T- test there was no significant different between WOMAC score with patellar malalignment.

Table 10 T-test in WOMAC score with patellar malalignment

Malalignment	WOMAC		
	n	Mean	p Value
Yes	28	40.14	0.711
No	8	38.13	0.751

DISCUSSION

Characteristic of Study Subject

The oldest of respondent was 69 years old and the youngest was 50 years old with mean 60.58 and group of age mostly 51- 60 years old related to risk factor for the occurrence of OA will increase after 50 years old. In this study, woman has a higher risk to suffer from OA (80.56%) than man (19.4%).

OA respondents with obese were higher (63.9%), which is appropriate with risk factor that OA often occurs in the people with overweight and obesity.^{8,13,15}

Frequency distribution of knee OA

AP and LAT radiograph of the knee become imaging method in diagnosing knee OA. In addition, the purpose of skyline projection is to see femoropatellar joint better than before. This study showed that knee OA in respondents had different in Kellgren-Lawrence grading of femorotibia joint and femoropatellar. Sixty seven knees were assessed out of 36 respondents, in which 5 respondents examined only 1 knee. Based on examination there was no isolated OAFT and isolated OAFP but all of them were combination of OAFT and OAFP. This is contrast with previous study of Szebenyi B et al. that out of 334 patients with knee OA, 218 had osteophyte in femoropatellar compartment and 184 had osteophyte in femorotibia compartment. Moreover, Duncan R et al. investigated 777 knee OA, and showed combination OA in femorotibia and femoropatella (4%), OA femoropatella (24%) and femorotibia (4%) and the remaining 32% showed normal radiograph while in this study only found combination of femoropatellar and femorotibia of knee OA . This difference may be due to differences in study area.^{1,3,4}

Based on previous study, OA of hip joint often occurs in black people and Asians. While in the United States, knee OA often occurs in Indian people than white people. This is related to differences in lifestyle, congenital abnormalities and growth.^{14,15,16}

Correlation between WOMAC Score with Kellgren Lawrence grading of knee OA with AP/LAT/Skyline knee projection

This study showed a positive correlation in Spearman's test with positive association with moderate power between pain and disability using WOMAC score to knee OA grading with AP/LAT/Skyline knee projection, in which higher of OA grading in knee so that WOMAC score. It took after Hunter DJ, et al. study which showed a significant correlation between WOMAC and Kellgren-Lawrence in knee OA, as well as Layon Peter study showed correlation between pain and osteophyte in knee joint .^{3,5}

Correlation between WOMAC Score with Kellgren-Lawrence grading of knee OA with AP/LAT knee projection

This study showed a positive correlation in Spearman's test with moderate power, between pain and disability using WOMAC score to grading of knee OA with AP/LAT knee projection, in which higher of grading knee OA so that WOMAC score. It took after Hunter DJ et al. study that showed a correlation between WOMAC and Kellgren-Lawrence in knee OA, as well as Layon's study which showed a correlation between pain and osteophyte in knee joint.^{3,5}

Correlation between WOMAC Score with Kellgren-Lawrence grading of knee OA with AP/Skyline knee projection

This study showed a positive correlation in Spearman's test between pain and disability using WOMAC score to grading of knee OA in AP/Skyline knee examination, in which higher of

knee OA grading so that WOMAC score. It took after Hunter DJ et al. study that showed a correlation between WOMAC and Kellgren Lawrence in knee OA, as well as Layon Peter study showed correlation between pain and osteophyte in knee joint.^{3,5}

Correlation between WOMAC score with grading in narrowing of femoropatellar joint space

There is a significant positive correlation with weak power based on Spearman's test between WOMAC score and grading in narrowing of femoropatellar joint space. It took after Hunter DJ et al. study that showed a correlation between WOMAC and grading in narrowing of femoropatellar joint.^{3,5}

Correlation between WOMAC score with patellar malalignment

The frequency distribution of patellar malalignment showed most of sample had lateral malalignment in 28 subjects (79.20%), medial in 1 subject (2.78%) and no malalignment in 7 subjects (19.44%). Based on stastical test with differential test (T-test) between WOMAC score and patellar malalignment showed no significant difference, which means hypothesis in this study was rejected.

In contrast, Hunter et al. study showed correlation between WOMAC score with patellar malalignment. Patellar malalignment is translation or patellar rotation deviation relative to the axis deviation across femoropatellar joint. Patellar malalignment often manifest as lateral high patellar tilt, lateral subluxation or combination of both. Soft tissue strength, medial retinaculum and lateral, joint capsule and ligaments were contributing to protect patellar adherence. Quadriceps femoral muscles consist of medial vastus and lateral vastus that protect optimal adherence of patellar. In healthy elderly was gained power from medial vastus and lateral relatively similar in various activities. Reduction in activities of vastus medial or increasing activity of lateral vastus caused lateral patellar malalignment and increase angle of lateral patellar tilt. Otherwise if there was depletion in activity of lateral vastus and reduction of medial vastus activity thus medial patellar malalignment will occur. But often occurs in lateral patellar malalignment, because in normal circumstances lateral vastus muscle relatively stronger than medial vastus.³ In this study, from 36 subjects only 29 subjects experienced malalignment, but there was no correlation with WOMAC score. WOMAC score assesses pain, stiffness and disability. While pain in OA affected by several factors: mechanical, bone, muscle, pain control, central nerve pain threshold differences.²⁵ This study conducted in Indonesia, which has different demographic compared to Hunter et al. study, possible that it leads to the differences in pain threshold. The difference in this study because Hunter et al. was using multicenter cohort method with new patients thus conducted evaluation in 2–5 years later and various demographic factors. This study was using analytical observational of cross-sectional method with new patients and old patients in one time that some of patients already done the treatment and physiotherapy.

Conclusion

There was a significant positive correlation with moderate power between knee OA grading in AP/LAT/Skyline examination with pain and disability using WOMAC score. There was significant positive correlation with moderate power between knee OA grading in AP/LAT examination with pain and disability using WOMAC score. There was significant positive correlation with weak power between knee OA grading in AP/Skyline examination with pain and disability using WOMAC score. There was significant positive correlation with weak power between grading in narrowing of femoropatellar joint space with pain and disability using WOMAC score. There was no difference in T test between patellar malalignment with pain and disability using WOMAC score, which is different from the previous studies because of demographic differences, research methods and sampling methods.

Limitations of the study are all sample with an OA combination femorotibia femoropatella, not obtained OA femoropatella isolated, this study was conducted in patients with partial old has undergone management therapy.

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Comorbidities in patients with gout in rheumatology clinic Dr. Hasan Sadikin general hospital in 2012 - 2013

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ABSTRACT

Background: Gout is a metabolic disease manifested mainly as an intense monoarticular inflammatory reaction which is strongly associated with hyperuricemia. Latest evidence showed that uric acid exerted effects on the development of other diseases. Many studies in developed countries had estimated the frequency of comorbidities associated with gout such as hypertension, obesity, diabetes mellitus, Chronic Kidney Disease (CKD), and Myocardial Infarct (MCI). However, no data regarding these frequencies have been found in Indonesia up to now to the best of the author's knowledge. This study aimed to establish the frequency of these comorbidities in patients with gout in Rheumatology Clinic Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Methods: All medical records of patients with gout in Rheumatology Clinic Dr. Hasan Sadikin General Hospital from January 2012 to December 2013 were collected. The data on blood pressure; Body Mass Index (BMI); random blood glucose, fasting blood glucose or 2 hours post prandial blood glucose; history of myocardial infarction; and creatinine were taken and analyzed to determine the presence of comorbidities

Results: Among all patients with gout in Rheumatology Clinic Dr. Hasan Sadikin General Hospital, 53.08% had chronic kidney disease, 42.73% had hypertension, 25.39% had diabetes mellitus, 15.70% had myocardial infarction and 12.22% had obesity.

Conclusions: Comorbidities commonly found in patients with gout in order of frequency were chronic kidney disease, hypertension, diabetes mellitus, myocardial infarct, and obesity.

Keywords: gout, comorbidities, frequency.

Introduction

Gout is a chronic disease affecting multiple systems which is caused by increased serum uric acid level (hyperuricemia). This condition contributed by error in purine metabolism or excretion is commonly further worsened by excessive purine intake.¹ Hyperuricemia leads to deposition and nucleation of uric acid into Monosodium Urate (MSU) crystals in synovial space which induces an inflammatory reaction and clinically manifested as an acute and very painful arthritis commonly known as gouty arthritis. Extremely or chronically elevated serum uric acid level also can lead to several derangements in the renal including chronic

urate nephropathy, acute uric acid nephropathy, and uric acid nephrolithiasis which eventually result in renal failure.²

Increasing concern into this disease was brought by the fact that the prevalence of gout and hyperuricemia remain large and had risen in the past 2 decades.³ During its natural course of disease, patients with gout and hyperuricemia are also associated with many comorbidities such as hypertension, Chronic Kidney Disease (CKD), obesity, diabetes, and Myocardial Infarct (MCI) probably due to recently found role of uric acid in pathogenesis of these comorbidities.⁴ Several studies had been performed in United States, United Kingdom, and Germany to estimate the frequency of comorbidities in gout population.^{5,6} However, to the best of the author's knowledge, similar data in Asia, particularly in Indonesia hasn't been documented. To address this issue, this study was designed to identify the frequency of comorbidities in patients with gout in Rheumatology Clinic Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Methods

In order to know the pattern of comorbidities in patients with gout, cross sectional study using all medical records of such patients in Rheumatology Clinic Dr. Hasan Sadikin General Hospital were carried out. The medical record of a patient would be included if the time of admission was between January 2012 – December 2013 and the patient was diagnosed with gout by attending physician or given code as ICD (International Classification of Disease) M10. Diagnostic criteria used for gout in Rheumatology Clinic Dr. Hasan Sadikin General Hospital were based on American College of Rheumatology guidelines. Several data were recorded for data analysis purpose such as age, gender, weight in kilograms, height in centimeters, blood pressure at the time of admission, blood glucose test (fasting blood glucose, random blood glucose, or 2 hours post prandial blood glucose), serum creatinine level, and history of myocardial infarction. All the data collected were then inserted into Microsoft Excel for analysis. Patients without any of the data above were excluded

The presence of particular comorbidities was checked according to the following definitions. Hypertension was defined as systolic blood pressure

more than or equal to 140 mmHg or diastolic pressure more than or equal to 90 mmHg.⁷ Obesity was defined as Body Mass Index (BMI) ≥ 30 kg/m² where BMI is body weight divided by height in meters squared.⁸ Diabetes was defined as either fasting blood glucose ≥ 126 mg/dl or the presence of diabetic symptoms (polydipsia, polyuria, polyphagia) and random blood glucose ≥ 200 mg/dl or 2 hours post prandial blood glucose ≥ 200 mg/dL.⁹ Chronic kidney disease was defined as estimated Glomerular Filtration Rate (eGFR) below 60 ml/min/1.73 m² where eGFR = $((140 - \text{age}) \times \text{weights (kg)}) / (72 \times \text{serum creatinine})$.¹⁰ History of myocardial infarction of each patients is recorded. Patients without the necessary data were not included in the data analysis of corresponding comorbidities.

Results

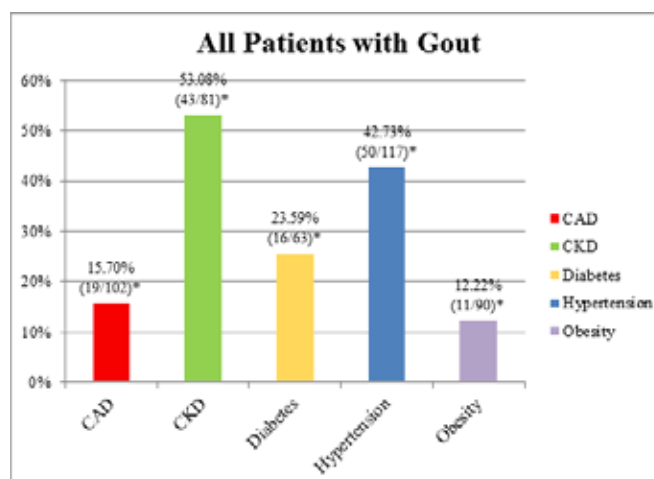
There were 128 patients who attended the Rheumatology clinic during period January 2012 – December 2013 and diagnosed with gout or ICD 10 code M10. Six patients were excluded from the data analysis due to the lack of data of interest. From these patients, 100 (81.96%) patients were male and 22 (18.03%) patients were female. Mean age of patients with gout was 58 with standard deviation 11.25 (Table 1).

Table 1 Patients Characteristic

Variable	n (%)
Gender	
Male	100 (81.96%)
Female	22 (18.03%)
Age	58 (SD 11.25)*

* Mean (SD)

There were 5 patients whose data were incomplete for blood pressure. Out of 117 patients, 50 patients (42.73%) that composed of 40 male and 10 female got hypertension. For BMI purpose, there were 32 patients who didn't have their height or weight measured. From 90 patients, 11 patients (12.2%) who consisted of 7 male and 4 female were obese. Fifty nine patients got no data about either blood glucose measurement or Diabetes history thus weren't included in the analysis of Diabetes. Among 40 patients which included, 16 patients (25.39%) consisted of 13 male and 3 female had Diabetes. There were 42 patients whose data were incomplete for determining eGFR, thus only 81 patients were included in the data analysis. From 43 patients (53.08%), there were 30 men and 6 women suffered from CKD. Coronary Artery Disease (CAD) was found in 13 male and 6 female (15.70%) out of 121 patients. (Figure 1)



*Numbers displayed (patients with comorbidities/ all patients with particular data regarding the comorbidities)

Figure 1 Comorbidities in Patients with Gout

Discussions

In this study, patients with gout had mean age of 58 (11.25) years. Nearly similar data also were presented by Mikuls *et al.* in their study of gout epidemiology that the mean age of patients with gout is 60.5 (15.4) years. Male predominance in this study, as commonly known in gout patients, was stated in that study as well (79.6%).¹¹

The most prevalent comorbidity in this study was CKD (53.08%) characterized by eGFR < 60 ml/min/1.73.² Different results were presented in studies carried out in United States by Zhu *et al.* in which hypertension (74%) was the leading comorbidities in gouty patients in the United States (US) while CKD (71%) was the second most.⁵ Many incomplete data in the analysis of CKD frequency could be the factor that influencing this discrepancies. Nevertheless, CKD had strong relation with gout based on the knowledge up to now. Kidneys act as the main excretory organs of these metabolism end products in such way that disturbance in the kidney function will decrease uric acid clearance and thus increase serum uric acid level.¹ Besides that, hyperuricemia could cause a downfall in kidneys' function through urate nephropathy, uric acid nephropathy, or nephrolithiasis which terminally lead to renal failure.

Hypertension occurred in 42.73% of patients with gout in this study compared with 74%, 17.5%, and 18.5% which stated in studies of gout comorbidities in US, United Kingdom (UK), and Germany respectively.^{5,6} These differences occurred probably due to the lack of data regarding anti-hypertension medication used which probably decrease the number of hypertensive patients in this study. Lifestyle variation in the population studied also contributed to these variations. Nevertheless, increased serum uric acid level is constantly associated with hypertension and many data and evidence support this. Pathogenesis of hypertension in hyperuricemia is related to the biological effects of uric acid in vascular such as to decrease Nitric Oxide (NO), increase Reactive Oxygen Species (ROS), induce vascular inflammation, and to induce proliferation of vascular smooth-muscle cells thus promote to vascular narrowing. In addition to vascular effects, uric acid

also exerts impacts towards renal such as increased renin, decreased NO, interstitial inflammation, interstitial fibrosis which all leads to vasoreactive hypertension.^{4,12}

Diabetes which occurred in 25.39% of all gout patients in this study is concordant with other study in Germany and US which was 25.9% and 26% respectively.^{5,6} Many studies had linked hyperuricemia with Diabetes Mellitus. One meta-analysis study had associated serum uric acid level with the risk of developing type 2 Diabetes and found that each 1 mg/dl increase in serum uric acid resulted in 17% higher risk of having type 2 Diabetes Mellitus.¹³ Uric acid had been found as mediator of proinflammatory imbalance in adipose cells by inducing ROS production via stimulation of NADPH oxidase and decreasing adiponectin production which is an important insulin sensitizer and anti-inflammatory substance.^{14,15}

Obesity was found in 12.22% patients with gout in this study which was smaller in frequency compared with the study in US (53%) and UK (27.7%).^{5,6} This discrepancy probably contributed by the lifestyle and socioeconomic level differences between the population studied. However, obesity had been associated with gout in study by Chen *et al.* who stated that obesity in women and hypertriglyceridemia in men could precipitate gout attacks in the absence of saturated serum uric acid level.¹⁶ It is also proved from the study in the United Kingdom general population that obesity was associated with higher risk of developing gout.¹⁷

The presence of CAD in 15.7% patients with gout in this study also stated by the studies in US, UK, and Germany (11.6%, 7.4%, and 5.8% respectively).^{5,6} Relationship between gout and coronary artery disease could be explained by the effects of uric acid towards vascular which is to cause endothelial dysfunction through reduction of NO and production of ROS.¹²

The results of this study are consistent with previous study carried out in US, UK, and Germany about comorbidities in patients with gout such as CKD, hypertension, diabetes mellitus, CAD, and obesity even though there were slight differences in the results obtained. Data regarding comorbidities of gout in Asia are lacking. These discrepancies probably caused by the differences in lifestyle and socioeconomic status of the population studied. Besides that, the incompleteness of data could be one of the factors affecting the differences. This study only address the most common comorbidities occurred in gout patients, while for the cause and effect relationship between gout and its comorbidities or vice versa cannot be determined. The results of this study can be used in the future as a step for further research about association between gout and its comorbidities. The consistent presence of comorbidities in patients with gout found in this study necessitates more meticulous comprehensive approach to gout management through early detection of these reported comorbidities and furthermore considering those comorbidities treatments' effects towards serum uric acid level and vice versa.

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Validity test of anti-c1q serum as diagnostic marker for lupus nephritis

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ABSTRACT

Background: Lupus nephritis is defined as renal involvement in systemic lupus erythematosus (SLE) patients and the most important cause of morbidity and mortality. The diagnostic criteria that used to diagnose lupus nephritis are 1997 American College of Rheumatology is 24 hours urine protein ≥ 500 mg and/or cellular cast, but significant renal damage can occur without proteinuria or cellular cast. Anti-C1q is an autoantibody that is produced by a chronic alteration of C1q collagen domain. Anti-C1q is a new specific marker for renal marker.

Objective: To determine the validity of anti-C1q serum by using 1997 American College of Rheumatology criteria as a gold standard.

Methods: This is a cross sectional study, conducted in October to December 2014 at Hasan Sadikin Hospital Bandung. The subjects had systemic lupus erythematosus with and without renal involvement, based on 1997 American College of Rheumatology criteria for SLE.

Results: There were 65 subjects included in this study, 64 subjects were female and 1 subject was male. The age average was 32 (SD 11.7) years old. As many as 66.2% subjects had been diagnosed with lupus erythematosus systemic at least 3 years. Twenty four hours urine protein was measured using spectrophotometry, urine sediment was examined for cellular cast, and anti-C1q serum was measured using micro enzyme linked immunosorbent assay. Based on American College of Rheumatology criteria, 34 subjects were classified as lupus nephritis group while 31 subjects were classified as non-lupus nephritis group. The area under the curve of anti-C1q was 0.610. The cut-off value used in this study was 10.43 U/ml. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of anti-C1q assay were 41.18%, 77.42%, 66.67%, 54.55% and 58.46% respectively.

Conclusion: Anti-C1q assay, based on this study, has a low sensitivity and medium specificity to detect lupus nephritis.

will suffer end-stage renal disease within the first 10 years.^{2,3} The presence of lupus nephritis significantly reduces survival to approximately 88% at 10 years.² Until now, lupus nephritis is still make a significant mortality and morbidity of SLE patients. Therefore, there is an urgent need for a lupus nephritis diagnostic marker.

Renal biopsy is the gold standard for lupus nephritis, however biopsy relatively expensive and need special equipment. Therefore, renal biopsy is not practical enough as a routine examination. The diagnostic criteria for lupus nephritis based on 1997 American College of Rheumatology (ACR) are 24 hours urine protein ≥ 500 mg and or cellular/granular cast. However the criteria has limitations, that significant renal damage can occur without proteinuria or cast in the urine.⁴ Anti-C1q is an autoantibody that is produced by a chronic change of C1q collagen domain. Anti-C1q only produced when C1q is in its bound form, therefore the pathological role of anti-C1q is local, and specific for lupus nephritis.^{5,6} Several studies had been conducted to investigate anti-C1q, however the studies are controversial. Moura et al.⁷ in 2011 found that anti-C1q serum has 86.66% sensitivity, 74.4% specificity, 52% positive predictive value, 94.59% negative predictive value for the diagnosis of lupus nephritis. Moura concluded that anti-C1q can be used as a lupus nephritis diagnostic marker therefore reduced renal biopsy. Meyer et al.⁸ in 2009 found anti-C1q serum has 100% sensitivity, 95.7% specificity, 100% positive predictive value, 50% negative predictive value. In contrary, Katsumata et al.⁹ found that anti-C1q serum level was correlated with lupus global activity and not correlated with lupus nephritis. Heindenreich et al.¹⁰ also found anti-C1q validity was lower than anti-dsDNA in diagnosing lupus nephritis. This study aimed to determine the validity of anti-C1q serum using 1997 American College of Rheumatology criteria for SLE as a gold standard.

METHODS

Study design

This is an analytical-observational study with cross-sectional design. The study was performed at Rheumatology Clinics/Division of Rheumatology of the Department of Internal Medicine and Clinical Pathologic Department at Hasan Sadikin General

Kidney is the most common organ involvement on systemic lupus erythematosus (SLE).¹ Approximately 55% of SLE patients developing nephritis during the first 10 years of disease and approximately more than 25% of these patients

Hospital, Bandung from October 2014 until December 2014. This study has passed the ethical clearance set by the ethical committee.

Subjects

The subjects of this study were patients that have been diagnosed as SLE with and without renal involvement based on ACR criteria and have been receiving immunosuppressant therapy, in Rheumatology Clinics at Hasan Sadikin General Hospital. The sample size was calculated using formula for diagnostic test. The minimal sample for this study was 65 samples. All participants have given consent to be enrolled in this study.

The inclusion criteria were SLE patients with and without renal involvement. The exclusion criteria were patients in their menstrual cycle; urinary tract infection; other glomerulopathies; inadequate 24-hours urine collection, serum with hemolysis, icteric or lipemia; icteric 24-hours urine. History taking was done in all patients to collect demographic characteristics and laboratory test according to the needs for data collection.

Blood, spot urine and 24-hours urine collection were performed to acquire necessary data. Serum was obtained from phlebotomy to measure anti-C1q. Serum was collected in the -20°C until the minimal sample acquired. Anti-C1q was assayed using indirect micro enzyme linked immunosorbent assay (Orgentec, Germany). The measurement scale is numeric.

Spot urine was collected from the midstream urine. Routine urinalysis and sediment analysis was performed for all subjects. Total urine creatinine was done before protein urine examination to determine 24-hours urine adequacy. Inadequate 24-hours urine was determined as ratio (predicted creatinine- total urine creatinine)/ predicted creatinine > 0.2. The inadequate 24-hours urine was excluded if the second 24-hours urine recollection was inadequate. Twenty-four hours urine protein determined by spectrophotometry.

The collection of the specimens was done at outpatient's laboratory, Clinical Pathologist Department, Hasan Sadikin Hospital. Routine urine examination and total urine protein was examined at Chemical Division, Clinical Pathologist Department, Hasan Sadikin Hospital. Anti-C1q serum was examined at Immunoserology Division, Clinical Pathology Department, Hasan Sadikin Hospital.

The data collected were processed using Statistical Package for the Social Sciences (SPSS) program. Kolmogorov-Smirnov test was used to describe the data distribution. Receiver operating characteristics was used to determined cut-off value and validity testing was used to determined sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

RESULTS

During the study timeline, *informed consent* was done to 85 subjects. Fourteen subjects were excluded because of urinary tract infection and 4 subjects because of menstrual period. Inadequate 24-hours urine collection was found in 5 subjects, therefore the collection was repeated. Three subjects

eventually met the criteria, while 2 other subjects were not met the criteria. Sixty five subjects were classified into 2 groups, which were 34 subjects with lupus nephritis and 31 subjects without lupus nephritis. The age mean in lupus nephritis group was 31.23 years old, while in non-lupus nephritis group was 34.43 years old. Characteristics of subjects are presented in Table 1.

Table 1 Characteristics of subjects

Variable	24-hours urine protein \geq 500 mg and or cellular cast (n=34)	24-hours urine protein < 500 mg without cellular cast (n=31)	p
Age (years old)			0.274*)
Mean (SD)	31.23 (11.17)	34.43 (12.25)	
Age at SLE diagnosed (years old)			0.582*)
Mean	27.31	28.73	
SD	10.01	10.75	
Gender			0.538**)
Male	1 (1.5%)	0 (0%)	
Female	33 (50.8%)	31 (47.7%)	
Duration of illness			0.385**)
< 3 years	14 (21.5%)	8 (12.3%)	
\geq 3 years	20 (30.8%)	23 (35.4%)	
Chief complaints			
Photosensitivity		2 (3%)	
Malar rash		7 (11%)	
Lupus hair		11 (17%)	
Arthralgia		5 (8%)	
Fatigue		5 (8%)	
Ankle edema		1 (1%)	
Without complaint		34 (52%)	

*) Independent t-test **) chi square test

n= total subject, SD = standard deviation, p= probability

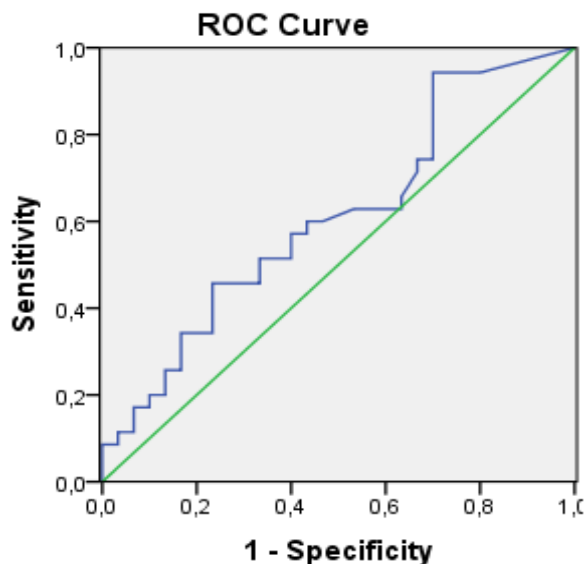
Sensitivity and specificity value for various anti-C1q cut off value are presented in Table 2. Cut off value used in this study is 10.43 U/ml with 40% sensitivity and 76.6% specificity.

Table 2 Sensitivity and specificity value for various anti-C1q cut off value

Anti-C1q cut-off value (U/ml)	Sensitivity (%)	Specificity (%)
\geq 1.10	94.3	23
\geq 2.15	94.3	30
\geq 2.35	88.6	30
\geq 2.55	85.7	30
\geq 3.05	74.3	30
\geq 4.05	62.9	46.7
\geq 5.76	51.4	66.7
\geq 6.91	45.7	70
\geq 8.00	45.7	73.3
\geq 10.43	40	76.7
\geq 12.22	37	76.7

Receiver operating characteristics curve for anti-C1q is presented in Figure 1. Area under the curve for anti-C1q was

0.610. Validity testing results for anti-C1q with cut off value 10.43 U/ml were 41.18% sensitivity, 77.42% specificity, 66.67% positive predictive value, 54.55% negative predictive value and 58.46% accuracy, is presented in Table 3.



Diagonal segments are produced by ties.

Figure 1 Receiver operating characteristics curve for anti-C1q

Table 3 Validity testing Anti-C1q in Lupus Nephritis

Variable	Lupus Nephritis		Total
	24-hours urine protein \geq 500 mg and or cellular cast (n=34)	24-hours urine protein < 500 mg without cellular cast (n=31)	
Anti-C1q			
Positive \geq 10.43 U/ml	14	7	21
Negative < 10.43 U/ml	20	24	44
Total	34	31	65

DISCUSSION

It is already known that lupus nephritis has higher incidence and prevalence among Asian patients, with lower survival rate. Renal biopsy is a gold standard for diagnosing lupus nephritis but biopsy is relatively more expensive than conventional parameters (urine protein and cellular/granular cast). However, significant renal damage can take place without proteinuria or cast. Therefore this study was aimed to determine the validity of anti-C1q as the new marker for lupus nephritis.

The age average of the subjects was 32.71 years old with 27.99 years old as the age average at the time of SLE diagnosed. This age average does not differs from other studies, which stated that SLE can occur at any age, but the most common age is 10-50 years old. Approximately 85% SLE happens before 50 and 20% happens in less than 16 years old. Younger SLE patients was correlated with worse prognosis and manifestation, especially renal manifestation.¹¹

The female gender was more common gender in this

study. Systemic lupus erythematosus was more common in female (83-97%) with 9:1 ratio. This ratio increased to 11:1 in reproductive age of the female. Although the exact etiology of SLE was not been determined, these fact causing a theory that hormonal factor acts as a risk factor for SLE.⁴

Majority of the subjects (66.2%) have been diagnosed SLE for \geq 3 years. Duration of illness was measured since lupus nephritis can develop in early and late onset of SLE. Lupus nephritis that occur during the early onset of SLE is one of the factor that determine worse prognosis of SLE.¹²

Photosensitivity, malar rash, lupus hair, is mucocutaneous manifestation of SLE, while arthralgia is musculoskeletal manifestation.^{13,14} Fatigue can happen in 50-90% SLE patients and can be related to depression or pain.¹⁵ Edema is one of renal manifestation, found in one subject which has proteinuria > 3500 mg/24 hours.¹²

Validity of anti-C1q Serum

Cut off used in this study is 10.43 U/ml since this value produced highest specificity, in line with the aim of this study. Cut-off 2.15 U/ml produced highest sensitivity but it cannot be used as cut off value since this value can be found in normal population (range 0.9 – 4.2 U/ml).¹⁶

The result of this study is different from Moura or Meyer study that showed a good sensitivity and specificity of anti-C1q serum. This study only showed moderate specificity (77.42%) and poor sensitivity (41.18%). Several factors may contribute to this discrepancy.

Twenty out of 34 subjects produced false negative value. False negative value will affect sensitivity value. False negative value can be explained by several factors, such as immunosuppressant and/or chemotherapy that have been given to the subjects. Immunosuppressant therapy is drugs that suppress immune response so it can alter anti-C1q serum level. Chemotherapy is an alkylating agent that induced cell death includes B cell. B cell reduction will also reduce anti-C1q serum level.

In some subjects, lupus nephritis was determined only by granular cast. Some subjects have urine protein range from 510.4-690 mg/dl. Urine protein level and urinary cast are used to determine the severity of lupus nephritis. Cai et al.¹⁷ stated that anti-C1q serum level positively correlated with renal damage level and there were significant difference between classes II, III and IV lupus nephritis. These subjects can be classified as class I or class II, with minimal renal damage, so that anti-C1q level possibly still low.

Other factor that may contribute to false negative results is anti-C1q binding as immune complexes in glomerulus. Mannik et al.¹⁸ found that anti-C1q/IgG ratio in glomerulus was 50 times higher than anti-C1q/IgG ratio in serum, therefore causing a lower level of anti-C1q in serum.

Proteinuria was used as gold standard in this study, however proteinuria has several limitations. Persistent proteinuria not always correlated with renal inflammation but can occur in urinary tract infection or other glomerulopathy. This condition had been excluded in this study.

Seven out of 31 subjects produced false positive results. False positive value will affect specificity value. These can

be explained by several factors. Proteinuria and/or cast were used as the gold standard in this study. Stine and Arenas stated a condition called silent lupus nephritis, condition, which significant renal damage occurs without proteinuria and or urinary cast.^{19,20} Stine found 4 out of 16 subjects were classified as class III and IV lupus nephritis by renal biopsy, but these subjects had normal creatinine and slightly increase urine protein. Other possibility of false positive result is increased disease activity in other organs. Katsumata et al.⁹ stated that anti-C1q serum was correlated with global lupus activity and not specifically correlated with active lupus nephritis.

The result of this study is different from other studies that produce a good validity of anti-C1q serum. The limitation of this study is using SLE patients that have been receiving therapy.

CONCLUSION

Based on this study, anti-C1q assay has a low sensitivity and moderate specificity to detect lupus nephritis, therefore anti-C1q serum cannot be used solely to detect lupus nephritis. The actual validity of anti-C1q serum to detect lupus nephritis is still to be proven in further studies.

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Effectivity and safety of mahkota dewa fruit extract compared to meloxicam (*phaleria macrocarpa fructus*) on osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is the most common musculoskeletal disease. World Health Organization (WHO) estimates that 10% of the aged over 60 year population have this disease. The aim of OA treatment is to reduce pain, which is the most OA patients chief complaint. People in Indonesia are very interested in use of herbal therapies from original traditional plant to treat pain now, one of the traditional plants that are known have a benefit is *Phaleria macrocarpa* or Mahkota Dewa fruit. *Phaleria macrocarpa* has been shown to decrease the degree of inflammation of OA animal model experiments. In order to know what is the effect of this fruit extract to reduce degrees of pain and change the levels of IL-1, IL-6, TNF- α in the blood as the marker of inflammation of patients with knee OA, and what is the effects to liver, kidney and haematology in the Indonesian population has not been investigated.

Methods: The research method is an experimental study and the research design is PROBE (Prospective Randomized Open End Blinded Evaluation), to evaluate the efficacy of the extract Mahkota Dewa fruit (*Phaleria macrocarpa fructus*) 330 mg (Super Mahkota POM TR 053 345 491) compared to meloxicam 7.5 mg in patients with knee osteoarthritis. The study population was outpatients with knee OA at Rheumatology Clinic Dr Hasan Sadikin Hospital Bandung. Patients are given *Phaleria macrocarpa* 330 mg or meloxicam 7.5 mg once a day for 14 days. Observations were made to evaluate the degree of pain as measured by VAS and Lequesne index at day 0, day 14 and measured again at day 28, after they are not taking the extract anymore.

Results: *Phaleria macrocarpa* 330 mg is equal to meloxicam 7.5 mg in reducing the degree of pain as measured by VAS ($p=0.78$) and the Lequesne index ($p=0.51$). Our finding, there is no effect of decreasing the proinflammatory cytokine IL-1 ($p=0.72$), IL-6 ($p=0.53$) and TNF- α ($p=0.07$) in the blood of both groups. Safety analysis shown that this extract is safe for consumption.

Conclusions: *Phaleria macrocarpa* 330 mg equal to meloxicam 7.5 mg in reducing the degree of pain however there is no effect on reducing proinflammatory cytokines in the blood of OA patients who had received therapy for 14 days in both groups. There is no adverse effects found on hematological, liver function and kidney

function after consumption this plant's fruit extract.

Keywords: osteoarthritis, mahkota dewa, *phaleria macrocarpa*.

Osteoarthritis (OA) is the most common musculoskeletal disease, where the pathogenesis is still not known well, but it is currently developing several hypotheses and theories are still debatable.^{1,2} OA formerly regarded as a non-inflammatory diseases caused by degenerative disease due to increasing age, but along with the development of research, it is known that OA is fairly complex disease, multifactorial causes, although the etiology is not well known, and the disease also occurs as a result of not severe acute inflammation.² World Health Organization (WHO) estimates that 10% of the entire population over the age of 60 years suffer from this disease. OA and other rheumatic diseases affecting more than 43 million people in the United States in 2020 and is expected to reach to 60 million patients.^{3,4} The study in UK shows the OA incidence is 25% per year, with the prevalence of disability due to knee OA is 10% and the severe disability as much as 5%.⁵

OA is also causing high socio-economic impact, both in developed countries as well as in developing countries, including Indonesia.^{6,7,8} It is estimated that one to two million elderly people in Indonesia suffer from disability due to OA. In the next century, the challenge of the OA impact will be even greater in elderly population.^{9,10} Currently, OA is characterized by the damage to the joint cartilage gradually accompanied by the presence of joint inflammation. OA can affect any joint, but is more common in the knees, hips, spine and hands.^{2,11-13} Pain is the main complaint of patients with osteoarthritis. Therefore, in general, the aims to the treatment of OA are to reduce pain, to prevent deformity, to improve quality of life, and to provide knowledge to the people about the disease.

The pathogenesis of OA is not only a degenerative process, but also inflammation. Joint pain, tenderness, limited range of motion, crepitus and swollen, increase intra-articular pressure,

changes in the structure of the joints and tissue debris cause inflammation of the synovial membrane, capsule, tendon, and bursa. Proinflammatory cytokines such as IL-1, IL-6 and TNF- α are found to be high in the synovial fluid of the knee OA patients.^{11,12,17,18}

Pharmacologic therapy in knee OA is divided into two main outcomes. The first, to reduce pain by analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections, steroids, hyaluronan acid. The second, drugs used to inhibit the progression of OA are Modifying Osteoarthritis Drugs (DMOADs). DMOADs work by maintaining structural balance and stimulate the growth of cartilage cells of cartilage. Several studies have found that these drugs also have anti-inflammatory effects.^{11,12,14,16}

Nowadays people are very interested in the use of herbal therapies derived from traditional plant. One of the traditional plants that are known to have benefits is Phaleria macrocarpa or mahkota dewa.^{19,20}

Mahkota Dewa fruit extract (Phaleria macrocarpa fructus) has been shown to reduce the degree of OA in animals, because the structure of the active substance similar to ketoprofen. Mahkota Dewa fruit ethanol extract with the doses of 15; 22.5; and 30 mg/kg bw mice can reduce levels of interleukin-1 β and TNF- α serum -induced arthritis in mice kolagen.^{21,22} Study in human clinical trials have not been conducted, but as a process of standardization we get a dose of Mahkota Dewa fruit extract 330 mg per day according to animal study doses.

Methods

The study design was an experimental research, the research design is Prospective Randomized Open-label Blinded at End Experimental (PROBE) to evaluate the efficacy of the mahkota dewa fruit extract 330mg (Super Mahkota, POM: TR 053 345 491) compared to 7.5 mg meloxicam as control group in patients with osteoarthritis.

The study population was patients with OA at the Rheumatology Outpatient Clinic in Dr. Hasan Sadikin General Hospital who live around Bandung city. Then sample was taken by simple random sampling methods to establish a research subject.

Inclusion criteria are patients with knee OA based on the consensus of the Indonesian Rheumatology Association (IRA), based on clinical (joint pain) and radiological (osteophytes), with at least 1 of the following 3 criteria: stiffness less than 30 minutes, age more than 50 years, crepitus on active joint motion; patients with OA pain intensity scores 2–7 according to Visual Analogue Scale (VAS). Exclusion criteria are there are other comorbidities: COPD, cardiac decompensation, walking disability was not caused by knee OA; undergoing medical rehabilitation; history of allergy to meloxicam or mahkota dewa; AST and ALT exceed twice the upper limit, normal creatinine > 1.1 mg/dl; using NSAIDs and oral or steroid injection 2 weeks or 3 months before the study.

Visual Analogue Scale (VAS) questionnaire is the most easy tool to be used by interviewer to determine the degree of pain that experienced by OA patients in numbers. Lequesne

index for knee OA, also known as (Index of severity for knee OA), was originally developed in French and also in other languages such as German, Korea and Singapore. This index has been studied can be used in Asia and has been proven valid in Southeast Asian populations. This index consists of 11 questions divided into three sections, five questions relating to pain, two questions about distance running, and four questions about the ability of daily activity or quality of life.⁴⁷

Radiological examination is sufficient to support the diagnosis, and also the degree of OA can be classified based on the radiological features. Semi-quantitative assessment done by Kellgren-Lawrence radiographic criteria and Osteoarthritis Research Society International (OARSI).⁴⁴

Test material in this study is the mahkota dewa fruit extracts that have been carried out which one of them is the standardization of assay in accordance with the applicable regulations in Indonesia. This herbal remedy has been registered, with the trademark “Super Mahkota”, which is registered under number : POM TR 053 345 491, in the form of capsules containing 330 mg of extract Phaleria macrocarpa each capsule.^{23,24}

Patients treated by Mahkota Dewa fruit extract capsules 330 mg once a day for 14 days, in the treatment group and 7.5 mg meloxicam once a day in the control group. Observations were made of the pain degree as measured by VAS and Lequesne index, which was performed before and after administration of Mahkota Dewa fruit extract. If the patients experienced pain during administration of the test material (VAS > 7), then they can be given an additional 500 mg paracetamol orally at the beginning to 4000 mg per day orally (rescue medication).

On day 1 and 14, blood samples were taken to measure the levels of IL-1, IL-6 and TNF- α . VAS and Lequesne index measured on day 14 and 28. Liver function measured with AST and ALT examination, renal function examination with ureum and creatinine, hematology examination with hemoglobin, leukocyte count, platelet count.

Kolmogorov-Smirnov test of Goodness of Fit performed to determine the normality of the distribution of the data. Statistical analysis done by t test for data ratio or interval scale who normally distributed. To compare the data pairs in the experimental group used the Wilcoxon Z test. Level of significance is determined by the value of p < 0.05.

Results

This study subjects were 42 patients. Six subjects were excluded from this study, because one person has other diseases like gout arthritis, one person does not follow the rules of taking the medication and four patients had dropped out.

Of the 36 patients who completed the study 19 patients had Mahkota Dewa fruit extract 330 mg in each capsules and 17 patients had Meloxicam 7.5 mg. Average age of knee OA patients was 59.1 years old. Most of the study subjects were women (85.7%), aged between 45 to 69 years old. The severity of radiological OA mostly located in the first degree (45.2%) and second degree (42.9%).

Table 1 Characteristics of OA patient according to group of treatment

Variable	Treatment Group Mean (SD)/N(%)		P value
	<i>Phaleria Macrocarpa</i> 330 mg	Control Meloxicam 7.5 mg	
Age (year)	60.24 (5.69)	58.10 (6.32)	0.26
Median	59.00	60.00	
Gender :			
Women	19 (90.5%)	17 (81.0%)	0.38
OA degree			
I	9 (42.9%)	10 (47.6%)	0.88
II	9 (42.9%)	9 (42.9%)	
III	3 (14.3%)	2 (9.5%)	
IL-1 (pg/ml)	4.01 (0.46)	4.03 (0.45)	0.82
IL-6 (pg/ml)	5.17 (5.97)	4.25 (4.53)	0.58
TNF- α (pg/ml)	27.06 (5.66)	25.92 (6.79)	0.56
Hb (gr/dl)	13.13 (1.01)	13.40 (0.96)	0.43
Leukocyt (/mm ³)	6936.84 (1816.35)	6662.50 (1209.34)	0.61
Trombocyt (x1000/mm ³)	279.26 (50.96)	271.38 (49.72)	0.65
AST (U/L)	24.79 (12.20)	20.81 (4.28)	0.22
ALT (U/L)	24.05 (14.40)	18.00 (6.30)	0.13
Urem (mg/dl)	29.50 (9.65)	22.81 (6.00)	0.02
Creatinine (mg/dl)	0.87 (0.39)	0.77 (0.17)	0.35
BMI	24.70 (3.72)	24.44 (3.20)	0.81

Inflammatory markers in patients who participated in the study were on average above normal limits levels, IL-1 with a mean of 4.05 pg/ml (SD 0.45), IL-6 with a mean of 4.72 pg/ml (SD 5.28) and TNF- α with a mean of 26.50 pg/ml (SD 6.19). Other laboratory test like haematological liver and kidney function are also within normal limits. Average of BMI were slightly higher with a mean 24.57 (SD 3.43) showed excessive load on the joints, which that is one of risk factor for OA. Table 1 shows there is no statistically significant difference between the groups of patients who get Mahkota Dewa fruit extract 330 mg compared with a control group who received 7.5 mg meloxicam, so the research results obtained to avoid bias due to sample selection are not the same set of characteristics. However ureum level is significantly different, where the group Mahkota Dewa fruit extract 330 mg had higher level with mean 29.50 mg/dl (SD 9.65) compared to meloxicam 7.5 mg, 22.81 mg/dl (SD 6.00) ($p = 0.02$), although the levels are still within normal limits.

The data distribution was normally distributed on VAS and Lequesne index group analyzed by using parametric statistics. Reduction in VAS data ($p = 0.009$) were not normally distributed, and the data is non-parametric, analyzed by the Wilcoxon test.

Table 2 Efficacy test after Mahkota Dewa fruit extract**(*Phaleria macrocarpa fructus*) 330mg treatment compared to meloxicam 7.5mg at day 14**

Variable	Day 14		P value
	<i>Phaleria macrocarpa</i> 330 mg N = 19 Mean (SD)	Meloxicam 7.5 mg N = 17 Mean (SD)	
VAS			
Before	40.48 (15.65)	36.75 (13.21)	0.42
After	24.47 (10.66)	19.71 (10.07)	0.18
Decrease	15.52 (10.39)	16.47 (10.42)	0.78
Lequesne			
Before	7.45 (2.87)	6.85 (2.32)	0.47
After	4.71 (2.58)	3.77 (1.73)	0.21
Decrease	2.55 (1.94)	3.03 (2.31)	0.51
IL-1 (pg/ml)			
Before	4.07 (0.46)	4.04 (0.45)	0.82
After	4.13 (0.63)	3.98 (0.41)	0.39
Decrease	-0.06 (0.54)	-0.01 (0.25)	0.72
IL-6 (pg/ml)			
Before	5.17 (5.97)	4.25 (4.53)	0.58
After	6.26 (9.47)	4.42 (5.26)	0.48
Decrease	-1.31 (8.16)	0.19 (5.88)	0.53
TNF- α (pg/ml)			
Before	27.02 (5.66)	25.91 (6.79)	0.56
After	27.32 (3.99)	27.88 (7.01)	0.77
Decrease	-0.26 (4.72)	-2.99 (3.86)	0.07

Table 2 shows that the mean VAS decrease after 14 days of Mahkota Dewa fruit extract 330 mg treatment was 15.52 (SD 10.39) did not differ significantly with meloxicam 7.5 mg 16.47 (SD 10.42) ($p = 0.78$). The VAS mean decrease $> 20\%$ so that it can be considered a significant reduction in the degree of pain. The mean decrease in Lequesne index after 14 days Mahkota Dewa fruit extract 330 mg was 2.55 (SD 1.94) did not differ significantly with meloxicam 7.5 mg, 3.03 (SD 2.31) ($p = 0.51$). Mahkota Dewa fruit extract 330 mg equivalent to 7.5 mg of meloxicam in reducing the degree of pain as measured by VAS and Lequesne Index. The effect of decreasing the proinflammatory cytokine in the blood are IL-1 -0.06 pg/ml (SD 0.54) compared to -0.01 pg/ml (SD 0.25) ($p = 0.72$), IL-6 -1.31 pg/ml (SD 8.16) compared to 0.19 pg/ml (SD 5.88) ($p = 0.53$) and TNF- α -0.26 pg/ml (SD 4.72) compared to -2.99 pg/ml (SD 3.86) ($p = 0.07$).

Table 3 Efficacy test after Mahkota Dewa fruit extract (*Phaleria macrocarpa fructus*) 330mg treatment compared to meloxicam 7.5mg at day 28

Variable	Day 28		P value
	<i>Phaleria macrocarpa</i> 330 mg N = 19 Mean (SD)	Meloxicam 7.5 mg N = 17 Mean (SD)	
VAS			
Day 28	22.37 (11.35)	18.35 (9.51)	0.26
Decrease	17.63 (10.05)	17.82 (7.97)	0.95
Lequesne			
Day 28	3.97 (2.07)	3.41 (2.35)	0.45
Decrease	3.29 (2.45)	3.38 (1.68)	0.89

The mean reduction in VAS still continues since day one

to 28 days in the group of Mahkota Dewa fruit extract 330 mg amounted to 17.63 (SD 10.05) did not differ significantly with meloxicam 7.5 mg 17.82 (SD 7.97) ($p = 0.95$), it also in the Lequesne index to 28 days in the group Mahkota Dewa fruit extract 330 mg mean decrease of 3.29 (SD 2.45) did not differ significantly with meloxicam 7.5 mg of 3.38 (SD 1.68) ($p = 0.89$). Mahkota Dewa fruit extract 330 mg is still giving the effect of lowering the degree of pain on day 28 of observation, despite being dismissed for 14 days.

Side effect of NSAIDs are gastrointestinal symptoms such as nausea 5.9% ($p = 0.28$) and heartburn 23.5% ($p = 0.03$), and cause some subjects were excluded from the analysis, while Mahkota Dewa the fruit extract have no any complaint. In a safety testing show that Mahkota Dewa fruit extract 330 mg is safe for consumption, because it does not interfere with liver function, renal function and hematology, and also blood pressure after taking the test material for 14 days.

After Mahkota Dewa fruit extract 330 mg treatment suspended for 14 days or at day 28 observation, when compared to meloxicam 7.5 mg, there is side effect on liver function, kidney function, and haematology. After day 28 observations, Hb of the subjects received 7.5 mg of meloxicam was decrease 0.47 g/dl (SD 0.51) compared to the group Mahkota Dewa fruit extract 330 mg 0.07 g/dl (SD 0.52) ($p = 0.03$)

Discussion

The long term pain in osteoarthritis need medications to reduce pain, but with lower side effects. Some pain medications such as NSAIDs have side effects on the gastrointestinal and cardiovascular systems.⁴⁵⁻⁴⁸ The use of herbs that have analgesic effect, is an option because of its low side effects. Some of the herbs have been studied to treat OA and is currently developed.⁴⁹⁻⁵⁵

Mahkota dewa is a plant that is widely used by people as a traditional medicine to treat various conditions as antimicrobial, anti-hypertension, anti-diabetes, anti-inflammatory and anti-cancer. These herbal drugs have other effects as an anti-oxidant that also may reduce pain in OA.^{23,24}

In OA progression chondro process will be disrupted due to several components such as proinflammatory cytokines IL-1, IL-6, TNF- α , metalloproteinase enzymes, and also the role of oxidative stress due to Reactive Oxygen Species (ROS).^{56,57}

Inflammation and cartilage degradation is one of the hypotheses of the pathogenesis of OA. Inflammation is caused by arachidonic acid metabolism and the role of various enzyme. While cartilage degradation is caused by an imbalance of proteases and protease inhibitors that leads to excessive degradation of cartilage matrix.² Oxidative stress causes damage to mitochondria that plays a role in the aging process, apoptosis, impaired function and tissue degeneration. Oxygen free radicals can penetrate into the cartilage and chondrocyte cells in vitro, although the actual chondrocyte cells can remain alive in a state without oxygen under normal circumstances, because it does not contain blood vessels. Chondrocyte metabolism itself is done anaerobically. Mitochondrial function in chondrocyte cells thought to

prevent free radicals into the chondrocyte cells. Free radicals are already entered into the chondrocyte itself will result in a decrease in the synthesis of extracellular matrix resulting in thinning of the joints and improve joint calcification resulting in the formation of osteophytes. It also will play a role in cell apoptosis of chondrocytes. Mitochondria have their own chromosome is a genetic component in cell metabolism. The presence of genetic mutations will lead to a more rapid degenerative diseases, which will accelerate the occurrence of OA at a younger age.^{56,57}

Pain that occurs in OA caused by three things: the inflammatory, ischemic and oxidative stress. Super oxide (SO) as free radicals also have an influence on tissue damage joints and cause pain. Phaleria macrocarpa also known to have antioxidant effects, therefore, anti-pain mechanisms presumably through suppression of this free radical oxidation pathway.^{56,57}

The degradation of matrix molecules is actually a part of the remodelling process in the growth, development and joint matrix turnover. The process is actually a physiological process, which is regulated by various cytokines, growth factors, and hormones that regulate the synthesis of proteinase inhibitors and thus are in a balanced state. Excessive proteolysis is a pathological process resulting from an imbalance between proteinases (MMPs) and inhibitors (TIMPs). If there is more matrix destruction, it will be a lot of fragments that have been unraveled as collagen, proteoglycans and calcium crystals, regardless of the synovium space, and cause inflammatory responses, the production of prostaglandins as the end result will be more and more so that the effect of pain will increase. Effects of prostaglandins alone which can lead to vasodilation of blood vessels, increase vascular permeability, cause pain with bradykinin potentiating effect, activating lymphocytes, platelet aggregation, bone resorption, and T-cell suppression. Bone resorption that occurs will cause fragments of calcium such as calcium pyrophosphate crystals, hidroxiapatit, and calcium phosphates went into the synovium. The degree of inflammatory response as a result of this study is usually mild. Pain occurs not only from the experience of OA joints, because the actual joint cartilage does not contain nerves and vessels, but pain can also come from tissue around the joints, such as tendinitis, bursitis, ischemic subchondral bone, muscle spasm, osteophytes, psychic, ligament disruption, and others. Therefore, the degree of pain reduction at Mahkota Dewa fruit extract 330 mg apart due to anti-inflammatory effects may be caused by the effects of antioxidants, the effects of other active substances are not known and may also have the effect of plasebo.⁵⁸⁻⁶⁰

This study showed no difference in inflammatory markers found in the serum of patients with OA who have given good treatment with Mahkota Dewa fruit extract 330 mg and Meloxicam 7.5 mg, although the degree of pain was reduced. The cause is probably due to the lack of high-dose or measurement of inflammatory markers IL-1, IL-6, TNF- α in OA should not be taken from the serum but directly from synovial fluid because there is no significant relationship between systemic inflammatory OA with local inflammation.

In the Framingham cohort study, years between 1998-2005 in 1235 obtained subject there was no significant relationship between markers of inflammation in OA.¹⁷ Placebo only actually has the effect to reduce levels of pain that is quite effective in OA.³⁰ In the other study found that the mean TNF- α and IL-1 β levels were lower in chronic OA compared with acute OA.⁴⁰ This differs from the type of inflammatory rheumatic diseases such as rheumatoid arthritis else (RA) which can be found higher levels of TNF- α , IL-6 and IL-1 in the serum. EULAR recommendations also provide non-pharmacological therapy in patients with a diagnosis of OA in addition to therapy with multiple drugs.⁶¹

Experimental research of traditional medicinal native plants in Indonesia, Mahkota Dewa fruit extract 330 mg given for 14 days in patients with a diagnosis of osteoarthritis showed effects can reduce pain by measurement of pain by VAS and Lequesne index. Patients with OA more than 60 years of age who may have renal impairment and cardiovascular disorders when NSAIDs treatment would be very dangerous can be given this treatment. Mahkota Dewa fruit extract is an therapeutic option for OA to reduce the degree of pain yet safe for the elderly.

The incidence of side effects of Mahkota Dewa fruit extract 330 mg against haematological, liver function, kidney function, or the blood pressure in the observation of the day 14 and 28 are not found. This shows that the mahkota of dewa fruit extract is quite safe. LD50 Mahkota dewa extract in mice is greater than 1500 mg/kg bw. There were no significant differences between the groups in toxicity in experimental animals given the extract preparations Mahkota Dewa than the control group.¹⁹

On day 28 observations obtained significant reduction in Hb subjects who received 7.5 mg of meloxicam for 14 days was 0.47 g/dl (SD 0.51), this shows the long-term administration of NSAIDs for more than 14 days can lead to a decrease Hb due to hidden gastrointestinal bleeding in a person over the age of 60 years as the average age of the study subjects.

Limitation of this study are time of this study was conducted with only a two-week observation period where as in studies using herbs, the new effect can be seen in a longer time around more than three weeks. Measurement of proinflammatory markers IL-1, IL-6 and TNF- α in two weeks has not been able to show a decrease in the blood levels, because the clinical symptoms will disappear earlier than the marker. In OA difficult to find increased inflammatory markers in the blood, but in the synovial fluid it can be higher than in the blood so that the examination in this study did not show significant results.

Conclusion

The conclusion of this study is Mahkota Dewa fruit extract (*Phaleria macrocarpa fructus*) 330 mg reduces the degree of pain in OA patients as same as meloxicam 7.5 mg. Mahkota Dewa fruit extract 330 mg does not reduce levels of IL-1, IL-6, TNF- α in patients with OA as well as the administration of meloxicam 7.5 mg. Mahkota Dewa fruit extract 330 mg does not impair kidney function, liver function and haematologic

parameters in patients with OA. Further research needs to be done about the content of some active substances *Phaleria macrocarpa* which acts as both an anti-inflammatory, and other effects that may influence the degree of pain decrease. Further research need to do to find the effects of *Phaleria macrocarpa* on levels of IL-1, IL-6 and TNF- α in the synovial tissue or joint fluid in different doses.

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Correlation of Random Urine Protein Creatinine (P-C) Ratio with 24-Hour Protein Urine in Lupus Nephritis Patients

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ABSTRACT

Background : Systemic lupus erythematosus (SLE) is a systemic autoimmune disease involving multiple organs including kidney and known as lupus nephritis (LN).

Lupus nephritis has a poor prognosis after a 10-years onset, more than 25% will be ended by end stage renal disease. There are glomerular and tubulointerstitial tissue damages due to immune complex deposits in LN which is activating inflammation cascade and causing disfunction of glomerular filtration and tubular reabsorption resulting proteinuria. In LN, proteinuria is used to diagnose, to assess the disease activity and to monitor the therapy. The gold standard of proteinuria is 24-hour urine protein examination, but the process of collecting in 24 hour urine is difficult, then the result is less accurate and reliable. Another alternative parameter is spot urine protein/creatinine ratio. Several studies have found a positive correlation between spot urine protein/creatinine ratio and 24-hour urine protein levels, but in LN, the results are various.

Objective. The aim of this study was analyzing the correlation between spot urine protein/creatinine ratio and 24-hour urine protein in lupus nephritis.

Methods. The study was conducted at Dr. Hasan Sadikin Hospital, Bandung, West Java, Indonesia in October 2014 to December 2014. The subjects were 45 patients with lupus nephritis based on the criteria of the American College of Rheumatology. The study analyzed correlation through cross-sectional model.

Results: The results of Spearman correlation test analysis showed a significantly strong positive correlation between spot urine protein/creatinine ratio and 24-hour urine protein levels in lupus nephritis ($r_s = 0.96$; $p < 0.001$). Based on the degree of proteinuria there was a strong positive correlation between spot urine protein/creatinine ratio and 24-hour urine protein levels in lupus nephritis significantly on the degree of protein < 1 g/24-h ($r_s = 0.91$; $p < 0.001$) and at 1–3.5 g/24-h ($r_s = 0.73$; $p < 0.05$).

Conclusion : There is a significant strong positive correlation between spot urine protein/creatinine ratio and the 24-hour urine protein levels in lupus nephritis, so it is recommended to use spot urine protein/creatinine ratio, as an alternative quantitative examination in lupus nephritis.

Keywords: lupus nephritis, 24-hour urine protein, spot urine protein/creatinine ratio

Background

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease involving multiple organs including kidney and known as lupus nephritis (LN). Lupus nephritis has a poor prognosis since after a 10-years onset, more than 25% will be ended by end stage renal disease. There are glomerular and tubulointerstitial tissue damages due to immune complex deposits in LN which is activating inflammation cascade and causing disfunction of glomerular filtration and tubular reabsorption resulting proteinuria.¹

In LN, proteinuria is used to diagnose, to assess the disease activity and to monitor the therapy. The gold standard of proteinuria is 24-hour urine protein examination due to the variation of protein excretion, but the process of collecting in 24 hour urine is difficult, such as patients adherence, an adequate collection and handling of this material in the laboratory. Because of those difficulties, the results sometimes are less accurate and reliable.²

Another alternative parameter is spot urine protein/creatinine (P-C) ratio. Random urine protein/creatinine ratio is the measurement in an untimed spot urine specimen, which avoids the influence due to variations of urinary solute concentration and provides a more convenient method to assess protein excretion. This method is also recommended by National Kidney Foundation and Kidney Disease Outcomes Global Improving (KDIGO) clinical guidelines for glomerulonephritis³.

Several studies have found a positive correlation between spot urine protein/creatinine ratio and 24-hour urine protein levels in pregnant woman, chronic kidney disease, kidney-transplantation and as well as in children but in LN, the results are various. Leung et al (2007)⁴ reported a good correlation and limits of agreement between the spot urine P-C ratio and 24 hour total protein levels across a wide range of proteinuria and recommended using the spot urine P-C ratio in screening and monitoring significant proteinuria in patients with LN. In opposition to this statement, Birmingham et al (2007)⁵ and Marques et al (2013)⁶ concluded that the random spot urine P-C ratio is unreliable in monitoring proteinuria changes in individual LN patients and is also unreliable as a screening test. They found that this method

underestimates and overestimates the results with about equal frequency. The aim of this study was analyzing the correlation between spot urine P-C ratio and 24-hour urine protein level in lupus nephritis.

METHODS

Study design

We conducted a cross-sectional study of urine excretion at Dr. Hasan Sadikin Hospital from October 2014 to December 2014. The study analyzed correlation through cross-sectional model.

Subjects

Based on sample calculation, the minimal sample was 37 subjects. This study found 45 patients for subjects with lupus nephritis based on the criteria of the American College of Rheumatology. They all had clinical and laboratory diagnosis history of lupus nephritis. Menstruation, others glomerulopathy, urinary tract infection, spot urine collecting over 2 hours and inadequate 24-hour urine were excluded. All participants gave consent to be enrolled in this study and the study protocol had been approved by the Ethic Committee and Health Research of Hasan Sadikin Hospital Bandung Indonesia.

Assessment

All subjects submitted 24-hour urine collections and random spot urine specimens. To determine the accuracy of the 24-h collections, the following formula was calculated (prediction creatinine content–measured creatinine content)/prediction creatinine content. The results >0.2 was deemed an under collection of 24-h urine or inadequate 24-h urine. Prediction creatinine content was measured by formula: $28-(0.2 \times \text{Age}) \times \text{Kg body weight for male}$ and $23.8-(0.17 \times \text{Age}) \times \text{Kg body weight for female}$. The P-C ratio was calculated, dividing the urinary proteinuria by creatinine. Urine protein and creatinine measurements were conducted in Clinical Pathology laboratory of Hasan Sadikin Hospital Bandung using automated analyzer (Cobas Integra). Total protein was measured using turbidimetry (pyrogallol red) method and creatinine using enzymatic colorimetric method.

Statistical analysis

Statistical analysis was performed by SPSS 18.0 Statistical Analysis (SPSS Inc. Chicago, IL, USA). In the univariate analyses which are the characteristics of the subjects' data were presented by mean, median, standard deviation, minimum and maximum. In the bivariate analysis which is determined the strength of the correlation was calculating by Spearman correlation coefficient (data were not in normal distribution). Two sided $p < 0.05$ was considered as statistically significant.

Results

A total 60 of 24-h urine samples were collected, with 15 samples were excluded for assessment because of inadequate 24-h urine collection. The remaining samples which could be assessed were 45 samples. The spot urine from 45 subjects

assessed for urinalysis and random urine protein creatinine ratio.

The baseline characteristics of lupus nephritis subjects are presented in Table 1.

Table 1 Characteristics of lupus nephritis subjects

Variable	% (n=45)	Mean (SD)
Age		32.23(10.91)
Sex		
• Female	97.79	
Onset of SLE		
• <1 year	22.23	
• $\geq 1-5$ years	33.27	
• $\geq 5-10$ years	36.61	
• ≥ 10 years	8.89	
Medication treatment	100.00	

The majority of subjects were female with mean age was about 32 years old. Early onset of glomerulonephritis in SLE was explained in onset of SLE less than 1 year (22.23%). All subjects already had medication treatment for lupus nephritis. The clinical and laboratory characteristics of lupus nephritis patients at the time urine was collected are described in Table 2:

Table 2 Clinical and laboratory characteristics of lupus nephritis subjects

Variable	n(%)	Median	Min-Max
Clinical features			
Malaise	6 (13.33)		
Fever	3 (6.67)		
Athralgia	3 (6.67)		
Malar Rash	4 (8.89)		
Lupus hair	4 (8.89)		
Photosensitive	1 (2.22)		
Peripheral edema	4 (8.89)		
Hypertension	21(46.67)		
Laboratory features			
Proteinuria	39 (86.67)		
Protein 24-h urine (mg/dL)		387.50	52.90–5800
Random P-C ratio		0.44	0.05–13.21
Granular Cast	17 (37.78)		
Microscopic hematuria	9 (20.00)		
Serum creatinine levels (mg/dl)		0.72	0.29–4.69
Estimated Glomerulus Filtration Rate/eGFR(mL/min)			
<60 mL/min	7 (15.56)		

Lupus nephritis subjects had non-specific symptoms which were malaise, fever, arthralgia, rash, lupus hair and photosensitive and specific symptoms for renal involved which were peripheral edema and hypertension. Laboratory features showed proteinuria was the majority followed by granular cast and microscopic hematuria.

Statistical analysis of correlation between random urine P-C ratio and 24-h protein urine in lupus nephritis is

represented by Spearman's (bivariate correlation) analysis between random urine P-C ratio and 24-h protein urine showed in Figure 1:

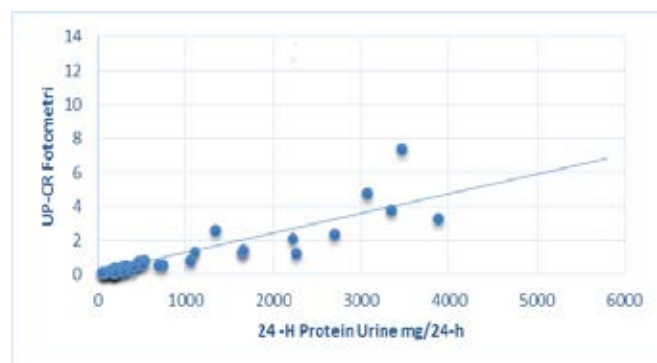


Figure 1 The correlation between amounts of random urine protein creatinine ratio and 24-h protein urine collections

Correlation between random urine P-C ratio and 24-h protein urine in a wide range showed an excellent positive correlation ($r_s=0.96$; $p<0.001$) in Figure 1.

Statistical analysis of correlation between random urine P-C ratio and 24-h protein urine in lupus nephritis sorted by class of proteinuria are represented in Table 3:

Table 3 Statistical analysis of correlation between random urine p-c ratio and 24-h protein urine in lupus nephritis sorted by class of proteinuria

Class of Proteinuria	n	Random Urine P-C ratio		r_s	P Value*)
		Median (mg/dl)*	Min-Max (mg/dl)		
Minimal Proteinuria (<1 g/24-h)	31(68.89)	0.20	0.05–0.78	0.91	<0.001
Moderate Proteinuria (1–3.5 g/24-h)	12 (26.67)	2.16	0.74–3.74	0.73	0.007
Severe Proteinuria (>3.5 g/24-h)	2 (4.44)	5.80	3.23–3.29	-	-

*)Kruskall Wallis Test, r_s = Spearman's correlation coefficient, p Value significant if $p \leq 0.05$

Based on the degree of proteinuria there was an excellent positive correlation between spot urine protein/creatinine ratio and 24-hour urine protein levels in lupus nephritis significantly on minimal protein or <1 g/24 h ($r_s = 0.91$; $p < 0.001$) and a strong positive correlation between spot urine protein/creatinine ratio and 24-hour urine protein levels in lupus nephritis significantly on moderate protein or 1–3.5 g / 24 h ($r_s = 0.73$; $p < 0.05$).

Discussion

This study result shows a positive correlation between random urine protein/creatinine ratio and 24-hour protein urine in

patients with lupus nephritis were significantly ($p < 0.001$) with the strength of correlation of 0.96 (excellent correlation). The result is consistent with the previous researches of random urine P-C ratio in lupus nephritis subjects. Nagasaki et al.⁷ in 2007 said that the results of the correlation between urine protein/creatinine ratio and 24-hour protein urine of each study would vary depending on the subject's disease, the target population and collecting time of the urine specimens. The results of researches showed a great positive correlation between urine P-C ratio and 24-hour protein urine levels in patients with lupus nephritis from different countries can represent various ethnic populations, so we can conclude that there were no differences in the results of the correlation between spot urine P-C ratio and 24-hour protein urine levels in patients with lupus nephritis by ethnicity/race. The collecting times specimens for spot urine P-C ratio either first morning urine or random urine as well give equally good results in studies of the correlation between spot urine P-C ratio and the 24-hour protein urine levels in patients with lupus nephritis.^{4,6,8,9} This study uses random urine specimen (untimed collection), because specimen is most commonly performed examinations, easy and convenient for the patient. This urine specimen can be collected at any time without the need for patient preparation prior research. Xin et al.¹⁰ in 2004 and Datta et al.¹¹ in 2013 mentioned the correlation between spot urine P-C ratio from first morning urine or random urine with 24-hour protein urine respectively each gave the same result, which was a strong positive correlation.

Previous research on random urine P-C ratio and 24-hour protein urine based on degree of proteinuria, gave different results. Birmingham et al.⁵ in 2007 had a weak agreement in proteinuria levels of 1 to 3.5 g/24-h and said that random urine protein/creatinine ratio could be used only in the minimal proteinuria level but could not be used in moderate proteinuria levels or flares. Marques et al.⁶ in 2013 had a weak correlation in proteinuria levels of <500 mg/24-h and there was no correlation in the range proteinuria of <1 g/24-h. Birmingham et al. and Marques et al. showed urine P-C ratio had underestimated or overestimated results for 24-hour protein urine levels. They concluded that the 24-hour protein urine assessment still have to be maintained to assess proteinuria in lupus nephritis.^{5,6}

This study provides different result against Marques et al. and Birmingham et al. The results of this study show an excellent positive correlation between urine P-C ratio and 24-hour protein urine either in groups of in minimal proteinuria (<1g/24-h), and a good correlation in the moderate proteinuria group (1 to 3.5 g/24-h) significantly. The results of this study reinforces the notion that the daily variation of the protein depends on the hydration status of individuals and then corrected by constant creatinine excretion will eliminate spurious results urine protein excretion rate and has an estimated rate approaching the estimated 24-hour total protein urine.

This research obtained the difference in the strength of the urine P-C ratio and 24-hour protein urine levels between groups of minimal proteinuria (<1 g/24-h) compared to

moderate proteinuria group (1 to 3.5 g/24-h). The strength of the correlation urine P-C ratio and 24-hour protein urine levels has decreased trend while the degree of proteinuria is more severe.

The reason alleged is due to the characteristics of proteinuria in lupus nephritis is different than proteinuria in chronic kidney disease non-SLE. Birmingham et al.¹² in 2008 mentioned that proteinuria in lupus nephritis was the type of hypoalbuminuria. Lupus nephritis is a disease with an inflammatory process as to found an increase in the albumin catabolism, resulting in decreased albumin in the blood and urine excretion. The situation is more severe as active lupus nephritis increases. Type of proteinuria in lupus nephritis is dominated by non-selective high molecular weight protein excretion. Assessment of proteinuria in lupus nephritis using urine reagent test pyrogallol red is more difficult to detect the type of proteins other than albumin, so the results could be underestimated.

Another reason is suspected because the majority subjects in lupus nephritis are female who have a smaller muscle mass. The production creatinine could be less, so the lower urinary creatinine excretion causes overestimated urine P-C ratio results.

The difference in results r_s (strength of correlation) between groups could also be caused by the possibility of bias which were differences the number of n between the 2 groups. Moderate proteinuria group which has less number of n ($n = 12$), so using a power test of 80%, would be obtained r_s is becoming smaller. It is possible if the number n in the 2 group of proteinuria are balanced then the value obtained r_s might be greater in moderate proteinuria group. Correlation value in the group of severe proteinuria (>3.5 g/24-h) is not obtained because the number of n is too small ($n = 2$). Based on the subject that urine protein 5800 mg/24-h has a value urine P-C ratio as 3.23 and subject that urine protein 3877.1 mg/24-h has a value urine P-C ratio as 3.29, but these are not yet drawn any conclusions about the correlation.

This study could not establish a regression equation for random urine P-C ratio because the data is not normally distributed. Previous studies obtained equivalent value of random urine P-C ratio and 24-hour protein urine levels in the values of 0.5; 1, and 3.5 g / 24 hours. Leung et al.⁴ mentioned that the value of random urine P-C ratio as 0.45; 0.7 and 1.84 mg / mg were equivalent to 24-hour protein urine values of 0.5; 1.0 and 3.5 g / 24 hours. Ginsberg et al.¹³ in 1983 mentioned the values of random urine P-C ratio as 0.2 and 3.5 represent the value of abnormal urine protein and urine protein nephrotic value.

Limitation of this study is the number n in the group of subjects based on the degree of proteinuria are not balanced, especially for subjects with severe proteinuria (nephrotic), so in this range could not be assessed the correlation of random urine P-C ratio. All subjects in the study had been

getting treatment, so that the study could not able to assess the correlation between random urine P-C ratio and 24 hours protein urine on before treatment condition.

Conclusion

There is a significant excellent positive correlation between random urine protein/creatinine ratio and the 24-hour urine protein levels in lupus nephritis, so it is recommended to use random urine protein/creatinine ratio, as an alternative quantitative examination in lupus nephritis.

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Myelopathy caused by Ossification of Thoracic Ligamentum Flavum

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ABSTRACT

Hypertrophy of the posterior spinal elements leading to compromise of the spinal canal and its neural elements is a well-recognized pathological entity affecting the lumbar or cervical spine. Such stenosis of the thoracic spine in the absence of a generalized rheumatological, metabolic, or orthopedic disorder, or a history of trauma is generally considered to be rare. Spinal ligaments, such as the ligamentum flavum (LF), are prone to degeneration and can lead to back pain and nerve dysfunction. Ossification of ligamentum flavum (OLF) is a pathological condition that cause neurological symptoms and usually occurs in the thoracic spine and less frequently in the cervical spine. However the disease is now being increasingly recognized as a cause of thoracic myelopathy. We report a rare case of thoracic myelopathy caused by OLF. A 48-year-old male presented with a chief complaint of weakness of bilateral lower extremities. Neurological examination revealed sensory deficit at Th 11 level below. Magnetic resonance imaging and computed tomography demonstrated OLF at the right T9–11 level. Thoracic myelopathy caused by OLF was consider and surgical intervention was performed. Posterior decompression and laminoplasty has been performed for this patient.

Key words: ossification of ligamentum flavum, thoracic myelopathy, laminoplasty

Introduction

Hypertrophy of the posterior spinal elements leading to compromise of the spinal canal and its neural elements is a well-recognized pathological entity affecting the lumbar or cervical spine. Such stenosis of the thoracic spine in the absence of a generalized rheumatological, metabolic, or orthopedic disorder, or a history of trauma is generally considered to be rare. OLF is the most common compressive factor contributing to thoracic myelopathy in Japanese, and was responsible for 60% of all thoracic cord compression either alone or combination with posterior longitudinal ligament ossification (OPLL) or in East Asia with an incidence rate between 2% to 4%, Males is predominance 2.2:1, and the highest prevalence was in their sixties followed by fifties and seventies^{1,2}

Ossification of the ligamentum flavum (OLF) of the thoracic spine is a pathological condition that causes neurological deficit usually occurs

in the thoracic spine and less frequently in the cervical spine.⁴ However the disease is now being increasingly recognized as a cause of thoracic myelopathy.^{5,6} Mechanical stress, growth factors and trauma of the spine contribute to accelerated ossification. OLF has been widely recognized as a main cause of thoracic myelopathy in Japanese patients. Few series are reported from Korea, China, India, Middle East, and Caribbean with sporadic case reports in Caucasians. It commonly involves lower thoracic spine (T9–T12) with upper thoracic spine (T1–T4) being the next common site.^{3,7-9} Herewith, we report case of OLF in Asian people that were treated in our hospital. The LF is an unusual elastic ligament compared to other spine ligaments because its high composition of elastic fibers. It functions as a passive stabilizing ligament, restoring the spine to a neutral posture following flexion and extension. This spinal ligament is high risk to calcification, ossification, and degenerative hypertrophy changes and the resultant thickening of the tissue has been implicated as a significant cause of stenosis. The LF is composed of elastin and collagen, approximately in a 2:1 ratio in humans. In several mammals the LF has been found to have an elastin content of 40–60%, including humans. This compares to approximately 1% in skin, 28–32% in the aorta, 3–7% in the lung, and 4% in the Achilles tendon. In destructive mechanical testing, a lacerated LF reduced the spine's resistance to flexion by 25%. In vitro studies revealed that the rupture strain for the LF averaged nearly 50%, as compared to 4–10% in the Achilles tendon, and 28% in the anterior cruciate ligament (ACL).^{10,11}

Liang ren et al in recent studies suggested that genetic modifications on numerous growth factors including BMP and TGF- β revealed their roles in regulating the development, growth, maintenance as well as the formation of new cartilage and bone tissues, Mobbs had demonstrated dietary habits may also be another independent risk factor. A patient with a low risk genetic background developed multilevel OLF as he followed standard Japanese dietary consumption of pickles (salted products) since young. Secondary to aging process, mechanical stress, disturbance in glucose metabolism, obesity, higher prevalence of diabetes mellitus and hyperinsulinism were observed in patients with OLF.^{4,7}

The mechanism of ligament ossification is classified into five types: Type I, laterally at the origin of the ligamentum flavum at the articular processes; Type II, from the lateral origin of the ligamentum flavum to the interlaminar portion of the ligamentum flavum; Type III, protrudes into the canal posterolaterally but is not fused in the midline; Type IV, consists of bilateral ossified ligaments that are fused at the midline with a groove at the fusion in midline; and Type V, the tuberos type, occurs when the fused ossified ligamentum flavum forms a “tuberos” mass posteriorly in the midline, which protrudes into the spinal canal. According to this classification only types IV and V would develop a myelopathy, and most of types I, II, and III would remain asymptomatic.¹²⁻¹⁴

Case Report

A 48-year-old male presented in our spine outpatient clinic complains of weakness of bilateral inferior extremities that gradually worsened over a period of ten years. On admission his muscle weakness 3/5 and hypaesthesia below the dermatome Th 11 was revealed. The reflexes were hyperactive in the lower extremities. Deep tendon reflexes were increased at and below the bilateral quadriceps femoris with myoclonus bilaterally. There was no urinary or bowel dysfunction. Plain x-rays of the thoracic spine failed to demonstrate any specific abnormality.



Figure 1 A. T1 weighted MRI of thoracic spine showed continuous OLF between T9–11. B. T2 weighted MRI showed OLF (double dagger). C. Canal stenosis on Axial T2 weighted image due to OLF (asterisk)

Magnetic resonance imaging (MRI) (Fig.1) of thoracic spine showed posterior compression of the dural tube, in the area corresponding to the ligamentum flavum, with cord compression at Th 9-11 levels. MRI showed enlargement of the ligamentum flavum at the Th 9-11 level and stenosis in the thoracic canal. No discal pathology was reported, T1- and T2- weighted MR imaging disclosed a hypointense mass posteriorly and dorsal in the anatomical place of the ligamentum flavum. The patient was operated and the lamina of the Th 9-11 vertebra and the enlarge masses were removed en bloc. These masses were connected with the tissue of the ligament the Th-9 and Th-11 lamina, with no fixation of the bony masses, causing compression of the thoracic cord and caused myelopathy. Histological result as the ligamentum flavum approaches its laminal insertion, it has uncalcified and then calcified fibrocartilaginous features.

Surgery

Surgical decompression by laminectomy and resection of the

hypertrophied ligaments must be made, supposed to be done as soon as possible after the onset of neurological symptoms and results can generally be improved. Many techniques of surgery can be performed: decompressive laminectomy and excision of the ligamentum flavum, laminectomy combined with lateral fusion, en bloc laminectomy is suitable for the treatment of lateral-type and diffuse-type OLF, and the separating laminectomy is suitable for the thickened, nodular-type OLF, decompressive laminectomy, laminoplasty and retaining posterior elements, fenestration, hemilaminectomy, and key-hole foraminotomy for the ossified lesions are advocated. In the present case, the patient underwent a posterior approach under general anesthesia in a prone position. A midline incision was made and the subperiosteal dissection until T8 to T12 lamina were exposed. Extensive drilling of the lamina T9 to T11 and then lamina removed, ossification of ligamentum flavum was drilled, and performed laminoplasty.^{4,9,12,13}

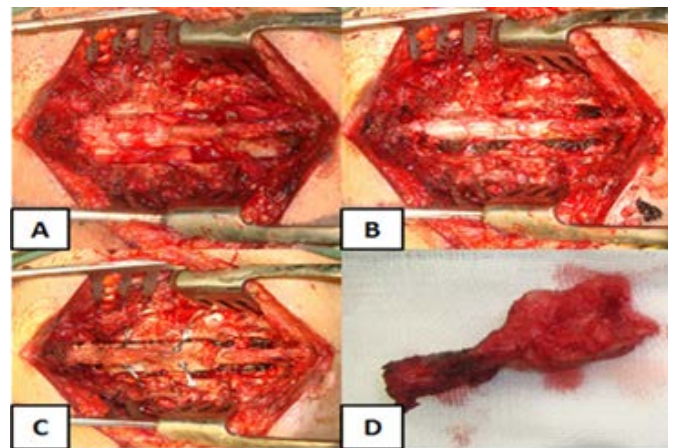


Figure 2 A After laminectomy, showed thickened and ossification of LF. B. Spinal cord decompressed after OLF was removed. C. Laminoplasty technique. D. Macroscopic OLF.

Histology specimen revealed that connective tissue fibres demonstrated penetrating the bone. The LF are made up chiefly of elastic connective tissue fibres longitudinally arranged with some thin bundles of collagen fibres and few spindle shaped fibroblasts. The elastic fibres are thinner than the collagen fibres. In the older age specimens, some fragmentation of elastic fibres was observed. Capillaries and very small thin walled blood vessels were not numerous and seen irregularly dispersed. No nerve trunks or endings were seen in the ligamentum flavum, osteochondral metaplasia and the presence of elastic fibers and chondrocytes (Fig 3)¹⁵. Patient underwent an intensive care unit stay for 24 hour, At hospital discharge day 6 patient remained paraparetic with a 3/3 muscular strength, mild hypoesthesia in both lower limbs. At 1 year, he was able to walk with a cane, with no sphincter or sensory alterations.

Discussion

OLF is a pathological condition that causes neurological symptoms and usually occurs in the thoracic and less frequently in the cervical spine. It is more common in East Asian countries and usually affects adults 40 to 60 years of age.

OLF is the most common compressive factor contributing to thoracic myelopathy in Japanese, and was responsible for 60% of all thoracic cord compression either alone or combination with posterior longitudinal ligament ossification (OPLL) or in East Asia with an incidence rate between 2% to 4%, Males is predominance 2.2:1, and the highest prevalence was in their sixties followed by fifties and seventies^{1,2}. Ligamentum flavum has two portions, the interlaminar and the capsular. Ossification usually begins in the capsular portion and spreads to the laminar portion. The mechanism of hypertrophy and progression of ossification is confined to ligamentum flavum (LF) only and does not extend to the neighbouring spinal bony arch. The commonest surgical techniques of this are posterior decompression and laminoplasty both has been described as an alternatives due to late neurological deterioration and pain secondary to postlaminectomy kyphosis⁷⁻⁹.

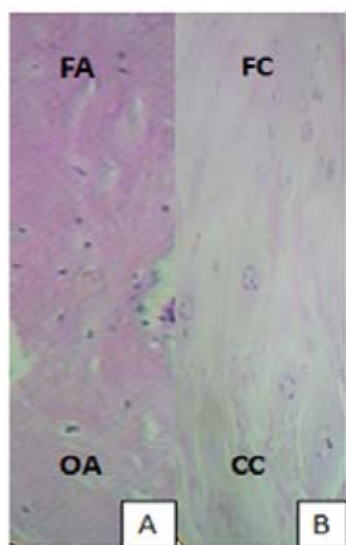


Figure 3 Histologic examination of the OLF. A. Section of the control ligamentum flavum showing a thin ossification front and regular arrangement of fiber bundles. B. From our patient the expanding ossification front, gathering many chondrocytes, and featuring an irregular of calcification.

FA: Fiber Area; OA: Ossification Area; FC: fibrocartilage; CC: Calcification Cartilage.

Ossification process starts at the base of the ligament with enchondral ossification of the vascularised fibrocartilaginous tissues. Studies have suggested cytokines as inflammatory marker, such as IL-6, TNF- α , seem to play a crucial role in OLF, IL-4, IL-10, IL-16 and TGF- β , contribute to the control of the magnitude to the inflammatory responses in vivo by the inhibition of the production of the pro-inflammatory cytokines or by counteracting many biological effects of pro-inflammatory mediators. Significant increases also in DNA synthesis and upregulated mRNA expression of types I, V, XI collagen and osteocalcin in LF cultures treated with various cytokines. LF cultures treated with IL-6, TNF- α , PGE2, and NO showed positive Von Kossa staining, indicating bone nodule formation from LF cells. There were also increased expression of TIMPs (Tissue Inhibitors of matrix metalloproteinase), especially TIMP-2, in ligamentum flavum

fibroblasts result in hypertrophy of the ligamentum flavum in spinal stenosis by inhibiting MMP activity, but not by causing proliferation of ligamentum flavum fibroblasts or inhibiting apoptosis of ligamentum flavum fibroblasts.^{4,7,10}

Numerous chondrocytes were present, especially around the calcification front, although no such chondrocytes were found in the normal ligamentum flavum suggested that the metaplastic chondrocytes in the ligamentum flavum are derived from mesenchymal cells or fibroblastlike cells, involvement of certain transcriptional factors in this process, Sox9, Runx2, Msx2 is known to promote chondrocyte differentiation of premature chondrocytes to hypertrophic chondrocytes and induces differentiation of premature mesenchymal cells and sometimes prevents the maturation of chondrocytes. In the normal ligamentum flavum, these factors might regulate chondrocyte differentiation, preserving homeostasis; however, overexpression of these factors in the OLF violates the regulation of chondrogenesis and differentiation of mesenchymal or fibroblast-like cells to mature chondrocytes in a complex autocrine/paracrine manner.^{3,4,16}

The underlying etiology and pathogenesis of OLF are still unknown. It has been documented that the incidence of thoracic OLF is higher in patients with diffuse idiopathic skeletal hyperostosis, fluorosis, diabetes mellitus, ankylosing spondylitis (AS), and ossification of the posterior longitudinal ligament (OPLL), metabolic diseases such as Paget disease, hypoparathyroidism and X-linked hypophosphatemia. When conservative treatment is not effective, surgical treatment should be considered.^{3,9} In native Indonesian 8.3% and Chinese Indonesians found 62.2% found that HLA-B27+ an allele of the major histocompatibility complex shows a strong association carry a greater relative risk related spondyloarthropathies (SpA) or AS, Indians (Asian) 2-6%, Japanese < 1% and Southeast Asians 5-12%.^{17,18}

Conclusion

Ossification of the ligamentum flavum has been widely recognized as a primary cause of thoracic myelopathy, even though the pathogenesis is still poorly understood. Mild symptoms should be conservative but if progressive neurologic deterioration surgery is mandatory. Further research and studies of OLF cases are necessary for early and proper diagnosis and therapy, in order to avoid a poor clinical outcome.

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