Bali Medical Journal (*Bali Med J*) 2017, Volume 3, Number 3 (IBL Conference 2017 Special Issue): S1-S6
P-ISSN.2089-1180, E-ISSN.2302-2914

Published by DiscoverSys

Ultrasound evaluation of nephritis, hepatic steatosis, and knee joint effusion in Balinese women with systemic lupus erythematosus

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ABSTRACT

Introduction: Organ involvement may influence the severity of systemic lupus erythematosus (SLE). Ultrasound (US) can detect organs morphological changes in SLE patients. Lack of data about US-detected lupus organs involvement triggered a research that explored the US findings of nephritis, hepatic steatosis, and knee joint effusion in Balinese women with SLE.

Method: This was an analytical cross sectional study to discover the prevalence of US-detected nephritis, hepatic steatosis, and knee joint effusion in Balinese women with SLE, and determined their association with clinical and laboratory findings. Anamnesis, physical, laboratory and US examination were performed. Correlations between clinical and laboratory results with US findings were tested using Spearman's correlation, linear regression and binary logistic regression tests ($\alpha = 0.05$).

Result: From 57 subjects, US nephritis was determined in 19 (33%) subjects, hepatic steatosis in 31 (54.5%) subjects, right knee joint effusion in 12 (21.1%) subjects, and left knee joint effusion in 14 (24.6%) subjects. No significant correlation between dyslipidemia and hepatic steatosis ($p>0.05$), but significant correlations between knee pain and knee joint effusion ($p<0.001$), between decreased of renal function with right and left nephritis ($p<0.05$) were noted. After adjusted with laboratory indicators, only the right nephritis showed significant association with decreased of renal function ($p<0.05$).

Conclusion: Nephritis, hepatic steatosis, and knee joint effusion were identified in Balinese women SLE patients using US. Some clinical and laboratory indicators had a significant correlation with knee joint effusion and nephritis, but most of the laboratory parameters demonstrated no significant association with hepatic steatosis.

Keyword: systemic lupus erythematosus, nephritis, hepatic steatosis, knee joint effusion, ultrasound
Cite This Article: Martadiani, E.D., Widiana, I.G.R., Dewi, D.A.R. 2017. Ultrasound evaluation of nephritis, hepatic steatosis, and knee joint effusion in Balinese women with systemic lupus erythematosus. *Bali Medical Journal* 3(3): S1-S6. DOI:10.15562/bmj.v3i3.712

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Received: 2017-07-01
Accepted: 2017-07-15
Published: 2017-07-17

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that may implicate many organs or systems. This disease can be found in all of ages and races, especially women. Worsening of the major organs function in SLE may be related to lupus or non-lupus associated causes. The manifestation of SLE in several organs may give serious complication, and some of them are life-threatening.

Renal involvement is one of the most serious complications of SLE and becomes a major predictor of poor prognosis.[1] More than 70% SLE patients have renal involvement. Renal involvement in SLE usually presents with abnormal urinalysis, proteinuria, and/or renal impairment. The incidence of renal involvement decreases patient survival to around 88% at ten years.[2] Renal involvement in SLE needs special attention to avoid progressivity of kidney function disturbance that culminates toward kidney transplantation or hemodialysis.

Cardiovascular disease is highly associated with metabolic disease especially dyslipidemia. In SLE patients, during three years of observation, there was increased prevalence of dyslipidemia from 30% into 60%.[3] Hepatic steatosis or fatty liver is significantly associated with metabolic syndrome, especially atherogenic dyslipidemia and diabetes mellitus (DM), and is suggested giving risk to the cardiovascular events.[4] Identify the meaning role of hepatic steatosis has encouraged an interest in its role in the progression of cardiovascular disease in SLE.

The musculoskeletal manifestation was found in almost all of the SLE patients, mostly arthritis or arthralgia.[5] Systemic lupus erythematosus may manifest as inflammatory polyarthritis, and it occurs in 70-95% of patients. Inflammatory arthritis is present at the time of diagnosis and becomes a common element of lupus flares.[6] Systemic lupus erythematosus may involve all joints, but the most affected joint is the hand and knees. Joint inflammation sometimes gives manifestation as joint effusion, and pain-related joint effusion may influence the SLE patient's quality of life.

Ultrasound (US) has the ability to detect morphological changes of intraabdominal organs and soft tissue of the joint as well. Thus, the presence of nephritis, hepatic steatosis, and joint

effusion in SLE patients can be evaluated accurately by the US. Unfortunately, there was a lack of data about US manifestation of kidney, liver, and knee joint involvement in Balinese women who suffered from SLE. The purpose of this study is exploring the US manifestation of nephritis, hepatic steatosis, and knee joint effusion in Balinese women with SLE, and finding the association of US findings with clinical and laboratory findings.

RESEARCH DESIGN AND METHODS

This was a cross sectional study to describe the prevalence of US findings of nephritis, hepatic steatosis, and knee joint effusion in Balinese women who suffered from SLE and to find the association of US findings with clinical and laboratory parameters. This study was done in Radiology and Internal Department, Sanglah Hospital, Denpasar. Ethical clearance was attained from Local Ethical Research and Development Commission of Udayana Faculty of Medicine-Sanglah Hospital Denpasar, Bali, Indonesia. The target population of this study was Balinese women with SLE. Accessible subjects were Balinese women with SLE who visited Allergy and Immunology Ambulatory Ward of Sanglah Hospital, Denpasar, Bali, Indonesia, during 6 months of the observation period. Inclusion criteria included the Balinese women older than 12 years old, who has diagnosed with SLE and agreed to participate in this study. Exclusion criteria consisted of heavy-drinking of alcohol, end-stage renal disease, and at the same time also suffered from an acute knee infection, during US examination had kidney abnormalities such as hydronephrosis, renal abscess, emphysematous pyelonephritis, kidney stone, or kidney tumor. Independent variables were decreased of kidney function, dyslipidemia and knee joint pain. Dependent variable were nephritis, hepatic steatosis, and knee joint effusion. Confounding variable was diabetes mellitus (DM). Subjects were collected using consecutive sampling. All subjects were performed anamnesis, physical examination, laboratory test and US examination. Anamnesis was included the parameters of exclusion criteria and degree of knee pain. Physical examination was done to discover the signs of a knee infection. Laboratory investigation included blood leucocyte count, total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), serum creatinine, and fasting blood glucose.

Diagnostic criteria of SLE is based on the criteria of the American College of Rheumatology (ACR) revised on 1977. Heavy drinking of alcohol was determined using criteria of Dietary Guidelines for Americans 2010, described as the consumption of more than 3 drinks on any day or more than 7 per week for women. End-stage renal disease was determined using the criteria of National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF/DOQI) 2002. Acute knee infection was defined as the presence of the clinical sign of infection of the knee that supported by leukocytosis. The degree of the knee pain was evaluated using 10 cm visual analog scale (VAS).

Decreased of kidney function was clarified if GFR < 60 mL/min/1.73 m^2. Criteria of DM is based on American Diabetes Association 2006. Dyslipidemia was an abnormality of lipid metabolism, characterized by increased of total cholesterol level (≥ 200 mg/dl), triglyceride ≥ 150 mg/dl, LDL cholesterol (≥ 100 mg/dl), and or decreased of HDL cholesterol level (HDL ≤ 40 mg/dl).[17] The presence of knee joint pain was explored and was classified in the dichotomic scale (present or absent).

Ultrasound examination was performed using Logiq S7 (GE®, USA). Liver US study was using a 3.5-5 MHz convex transducer on the B-mode setting. It started using subcostal approach to determine the liver size, liver echo parenchyma, and hepatic vein. The measurement was conducted on a sagittal approach in the mid clavicular line, from the diaphragm to the inferior border of the liver. The intercostal approach was conducted to evaluate the liver echo parenchyma and portal vein. Liver evaluation included liver size, echogenicity of liver parenchyma, echogenicity of walls of the portal and hepatic vein, and visualization of the deep portion of the liver. Scanning of the spleen also done to compare liver and spleen echogenicity. Hepatomegaly was enlargement of the liver, measuring more than 14 cm at the right liver lobe. Ultrasound manifestation of hepatic steatosis was described as increased liver echogenicity, and beam attenuation resulted in relatively hypoechoic of renal cortex compared to liver parenchyma, increased echogenicity relative to the spleen, absence of the normal echogenic walls of the portal and hepatic vein, and poor visualization of the deep portion of the liver.[8] Kidney US examination was using similar transducer on the B-mode setting. For the right kidney, the patient laid in the supine position, the transducer was placed in the right lower intercostal space in the midaxillary line. For the left kidney, the patient lied supine or in the right lateral decubitus position, the transducer was in the lower intercostal space on the posterior axillary line. Evaluation of the kidney included the renal size, renal parenchymal echogenicity, prominence of the renal pyramid, parenchymal calcification, presence of calyceal dilatation, stone, space occupying lesion (mass or abscess) of the kidney parenchyma or renal sinus, and fluid in the perirenal spaces. Normal kidney

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size was 8-13 cm. Nephritis was described as increased kidney, hyperechoic compared to the liver echo parenchyma, or it had similar echogenicity with renal sinus. Renal abscess described as a well-defined hypoechoic area within the cortex or in the corticomedullary parenchyma with internal echoes, sometimes associated with perinephric collection. The kidney stone was described as echogenic foci related to acoustic shadow in the renal collecting system.[9] Emphysematous pyelonephritis was described as enlarged kidney with coarse echoes within renal parenchyma or collecting system, or the presence of dirty echogenic foci with reverberation/ring-down artifacts representing air.[10] Kidney tumor was defined as a solid or partially cystic lesion in the kidney. Knee US examination was using a linear transducer, 10 MHz frequency, B-mode setting. Knee US procedure performed in the supine position, flexion knee, adapted from EULAR part I.[11] Knee joint effusion was defined as ≥ 4 mm effusion depth.

Statistical analysis included descriptive statistic to describe the prevalence of US nephritis, hepatic steatosis, and knee joint effusion in Balinese women with SLE. Correlations between decreased of kidney function and US-nephritis, dyslipidemia and hepatic steatosis, also knee pain and knee joint effusion were tested using Spearman correlation test. Binary logistic regression was used to determine the association between US-nephritis with decreased of kidney function and DM, hepatic steatosis with increased total cholesterol level, increased LDL level, increased triglyceride level, decreased HDL level and DM. Correlation of the depth of knee joint effusion and degree of knee pain was tested using linear regression test. All of the statistical analysis was using 95% confidence interval (CI).

Tabel 1 Subjects characteristic

Parameter	Mean or percentage (n=57)
Age (mean ± SD)	33.2 ±10.7
Clinical characteristic :	
Duration of illness (month; mean±SD)	45.46 ± 38.71
Presence of knee pain : Right knee	6 (10.5%)
Left knee	9 (15.8%)
Laboratory results (mean ± SD) :	
Leucocyte (plp x 1000)	9.48 ± 4.84
Total cholesterol (mg/dL)	207.79 ± 54.86
Triglycerida (mg/dL)	164.89±126.07
LDL (mg/dL)	113.93±42.83
HDL(mg/dL)	56.64±15.58
Serum creatinine (mg/ dL)	0.88± 0.37
Fasting blood glucose (mg/dL)	95.28 ± 23.52
Comorbid disease :	
Diabetes mellitus	4 (7%)
Dyslipidemia	34 (59.6 %)
Hypercholesterolemia	27 (47.4%)
Hypertrigliceridemia	21 (26.8%)
High LDL	8 (14%)
High HDL	5 (8.8%)
Decreased kidney function (GFR<60mL/min/1.73 m^2)	6 (10.5%)
Ultrasonography results :	
Liver size (mean ± SD)	12.68 ± 1.13
Hepatomegaly	7 (12%)
Hepatic steatosis : Present	31 (54.5%)
Absent	26 (45.6%)
Kidney size (mean ±SD) : Right kidney (cm)	9.80 ± 0.89
Left kidney (cm)	9.99± 0.96
Presence of nephritis : Right kidney	9 (15.7%)
Left kidney	13 (22.8%)
Right knee joint effusion: Present	12 (21.10%)
Absent	45 (78.95%)
Depth of effusion (mm)	8.94 ± 4.51
Left knee joint effusion: Present	14 (24.6%)
Absent	43 (75.4 %)
Depth of effusion(mm)	8.15 ± 4.9

RESULT

57 subjects participated in this study (Table 1), all of them are Balinese women, and 95% of them are 15-49 years old. The subject age range was 15-57 years old. Duration of illness varied from 3-168 months. All of the subjects with knee pain did not reveal signs of infection on their knees nor leukocytosis on blood examination. Their comorbid diseases included DM (7%), dyslipidemia (59.6%), and decreased kidney function (10.5%).

Ultrasound detected nephritis of the right and left kidney was found in 9 and 13 subjects (15.7% and 22.8%, respectively). Regardless of the right or left side, nephritis was found in 19 subjects (33%). None of the kidneys had abnormal size. All of the nephritic kidneys showed increased echogenicity of the renal parenchyma. Prominent renal pyramid of the right kidney was seen in 6 subjects (11%), and the left one was observed in 4 subjects (7%). One of the left kidney (2%) contained calcifications in the renal parenchyma. There was no calyceal dilatation, renal stone, space occupying lesion such as renal mass or abscess in the kidney parenchyma or renal sinuses, nor fluid in the perirenal spaces.

Hepatic steatosis was detected in 31 subjects (54.5%). The normal liver size was seen in 50 subjects (88%), hepatomegaly was noted in 7 subjects (12%). Twenty-six subjects (45.6%) had normal liver echogenicity, and 31 subjects (54.5%) had increased liver echogenicity. Distinct echogenicity of the wall of the portal and hepatic vein was seen in 30 subjects (52.6%), and 27 (47.4%) subjects had indistinct echogenicity. Good visualization of the deep portion of the liver was seen in 42 subjects (74%), and poor visualization was noted in 15 subjects (26%).

Table 2 Correlation of clinical and laboratory results with ultrasound findings in Balinese women with SLE

Variables	r	p value
Hepatic steatosis and dyslipidemia	0.002	0.737
Right nephritis and decreased of renal function	0.14	0.004*
Left nephritis and decreased of renal function	0.08	0.039*
Right knee joint effusion and right knee pain	0.52	<0.001*
Left knee joint effusion and left knee pain	0.42	<0.001*
Depth of right knee joint effusion and degree of right knee pain	0.55	0.006*
Depth of left knee joint effusion and degree of left knee joint	0.74	<0.001*

**: significant (p<0.05); r: correlation coefficien*

Table 3 Association of Indicators of Dyslipidemia and Diabetes Mellitus with Hepatic Steatosis in Balinese Women suffered from SLE

Variable	B	p value	CI
High total cholesterol level	1.18	0.09	0.821- 12.994
Low HDL level	1.31	0.28	0.342 - 39.941
High LDL level	-0.57	0.41	0.146 - 2.202
High triglyceride level	-0.59	0.35	0.165 - 1.884
Diabetes mellitus	0.95	0.45	0.225 -29.494

**: significant (p<0.05); B: constanta; CI: confidence interval*

Table 4 Association of Decreased of Renal Function with Right and Left Nephritis after Adjusted by Diabetes Mellitus in Balinese Women with SLE

Variable	B	p value	CI
Right nephritis			
Decreased of renal function	2.557	0.01*	1.720 - 96.726
Diabetes mellitus	1.053	0.39	0.249 - 33.065
Left nephritis			
Decreased of renal function	1.74	0.08	0.836 - 38.880
Diabetes mellitus	-19.87	0.99	0.000 - 0.000

**: significant (p<0.05); B : constanta; CI: confidence interval*

Right knee joint effusion was found in 12 subjects (21.1%), and left knee joint effusion was noticed in 14 subjects (24.6%). Eleven subjects (19.3%) suffered from the right and left knee joint effusion simultaneously. Mean of effusion depth of the right knee was bigger than the left knee (8.94 ± 4.51 cm vs. 8.15 ± 4.9 cm, respectively). The degree of the knee pain was ranged from VAS 3-9.

Several ultrasound findings showed significant correlation with a clinical sign and laboratory findings. There were positive weak significant correlations between right and left nephritis with decreased of renal function (r=0.14; p<0.05 for the right nephritis, r=0.08; p<0.05 for the left nephritis, respectively). Moderate correlations were found between right and left knee joint effusion with knee pain (r=0.52; p<0.001 for right knee joint effusion, r=0.42; p<0.001 for left knee joint effusion, respectively). There was no significant correlation between hepatic steatosis and dyslipidemia (r=0.002; p>0.05) (Table 2).

Diabetes mellitus and several indicators of dyslipidemia such as high total cholesterol level, high triglyceride level, high LDL level and low HDL level were also showed non-significant association with hepatic steatosis (p>0.05) (Table 3). The same findings also were shown by the association of DM and decreased of renal function with left nephritis (p>0.05) (Table 5). Decreased of renal function was still showed a significant association with right nephritis (p<0.05) without the influence of DM as confounding variable (Table 4). Significant correlations were seen between the depth of knee joint effusion and degree of knee pain (r= 0.55; p<0.006 for the right knee and r =0.74; p<0.001 for the left knee, respectively).

DISCUSSION

This study only involved Balinese women with age ranged from was 15-57 years old, and 95% of them were child bearing age. This study showed the parallel result in subject age range with the previous reference, which mentioned that the peak age at onset of SLE approximately 20-40 years of age, while distinctly it can occur in all ages.[12] This condition may associate with increased plasma estrogens and low plasma androgens in women during her reproductive phase. Estrogens enables humoral response that causes upsurge proliferation of B cell, prolongs the survival of autoimmune cells, and triggering B cells to produce antibody.[13]

The manifestation of renal involvement in SLE is variable. It could be asymptomatic hematuria or proteinuria, renal impairment, or end stage renal failure. Until 65% renal involvement manifests as nephrotic syndrome, and also a nephritic syndrome. Kidney failure is usually found in SLE patients, may be due glomerulonephritis or acute tubulointerstitial injury. The International Society of Nephrology and the Renal Pathology Society (ISN/RPS) arranged a revised classification based on the clinicopathological information, from class I until class VI.[14] Numerous clinical and laboratory findings were considered as prognostic importance (such as hypertension, an elevated serum creatinine, and a low serum C3 level), but renal biopsy is still crucial for determining whether a patient required treatment.[15] Renal biopsy classified Lupus Nephritis in several classes: Class I and II are used for purely mesangial involvement, class III for focal glomerulonephritis with subdivisions for active and sclerotic lesions; class IV for diffuse glomerulonephritis; class V for membranous lupus nephritis; and class VI for advanced sclerosing lesions.[14]

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Ultrasonography is a safe, noninvasive imaging modality that is commonly used to assess kidney, especially to check the change in cortical echogenicity as a manifestation of vascular, glomerular, and tubule interstitial lesions as a cause of renal involvement in SLE. The limitation of US is it can detect nephritis but unable not differentiate the histologic classes of lupus nephritis.[16] This might be the cause of the wide variability of renal manifestation and equivalent US manifestation in different classes of histological manifestation of lupus nephritis. This study found that there were weak positive significant correlations between right and left nephritis with decreased of renal function, and after adjusted by DM as a confounding variable, the only nephritis of the right kidney showed significant association with decreased renal function. Stanley et al. are studying ultrasonography findings in Lupus nephritis classified the cortical echogenicity and subsequently correlated them with clinical and histopathology findings. They reported that ultrasonography was 95% sensitive for recognition the clinically SLE nephritis. There was a significant correlation between abnormal kidney size and cortical echogenicity with a degree of renal insufficiency in Lupus nephritis. But they also found that there was no correlation between glomerulonephritis histologically and the class of cortical echogenicity.[17]

Liver involvement is usually not a part of the SLE spectrum, but it is seen in up to 60% of SLE patients.[18] Liver involvement of SLE may be associated with wide range of factors such as drug induced liver damage, hepatic steatosis, viral hepatitis, vascular thrombosis, and overlays with autoimmune hepatitis (AIH) or due to SLE itself.[19] This study found the prevalence of US-detected hepatic steatosis in Balinese women with SLE was 54.5%. Based on liver histological findings in SLE patients, several previous retrospective studies showed that steatosis was commonly found in SLE patient in various proportions.[18-20] Huang et al. (2012) reported from 134 SLE patients who underwent assessment by a hepatologist, imaging investigation, and liver biopsy identified 31 cases of fatty livers, 35 cases of drug-induced hepatotoxicity, ten autoimmune, etiologies, and 3 cases of viral hepatitis.[21] Matsumoto et al, investigated liver histology of 73 SLE patients, and recognized that fatty liver was the main feature in 72% of them, followed by nodular regenerative hyperplasia, viral hepatitis, primary biliary cirrhosis (PBC), and autoimmune hepatitis (AIH) (6.8%, 4.1%, 2.7%, and 2.7%, respectively).[20]

Hepatic steatosis is also categorized by atherogenic dyslipidemia, postprandial lipemia, and high-density lipoprotein (HDL) dysfunction. This study was trying to prove the correlation between hepatic steatosis with dyslipidemia, but the statistical analysis result showed no significant correlation. There was also no significant association between DM and each component of dyslipidemia such as hypercholesterolemia, high triglyceride level, high LDL level and low HDL level with hepatic steatosis. Hepatic steatosis in this study might be not related to dyslipidemia but could be influenced by other factor related to SLE (i.e. medication such as methotrexate or corticosteroids), but it still needed further investigation.

Knee joint involvement is commonly seen in SLE. This study found that right knee joint effusion was detected in 21% subjects, and left knee joint effusion was found in 25% subjects. Ossandon et al. evaluated ultrasonographic alteration in SLE knees and reported that knee joint effusion was seen in 12 (23%) knees.[22] A systematic review of US evaluation of SLE joints by Lins and Santiago based on seven databases ranged from 1950 to January 2015, reported that from a total of 888 hands and wrists, 154 ankles/feet, and 56 knees, there were effusion was identified in 602 joints, synovitis in 213, tenosynovitis in 210, synovial hypertrophy in 150, and bone erosions in 73 cases. They found that US examination detected musculoskeletal alteration on a higher frequency than observed on clinical finding.[23] Some references also found that ultrasound could detect subclinical joint inflammation in SLE especially in the hand, wrist and the feet.[24,25] This study found a significant moderate correlation between right and left knee joint effusion and knee pain, and a significant moderate to good correlation between the depth of right and left knee joint effusion with degree knee pain. Knee pain in SLE may associate with arthritis or synovitis, myalgia or myositis, tendinosis, or osteonecrosis. Instead of knee joint effusion, this study did not investigate another possibility of the knee pain origin. Based on the correlation between the depth of joint effusion with knee pain, more the amount of joint effusion, it would cause more capsular knee joint distension and stimulated a higher degree of knee pain. Evaluating joint changes especially knee joint effusion in SLE patient could be done accurately using the US, and it might give related data to the clinician.

In this study, we did not evaluate the histopathology of Lupus involvement in the kidney. It gave consequences that we could not compare every class of Lupus nephritis with our US findings. Instead of knee joint effusion, we did not investigate other anatomical alteration such as bone and other soft tissue changes on the knee joint so that we could not explain about the possibilities of another source of knee pain. Those conditions were the limitation of this study, and further research was needed to explain their role in SLE patients.

CONCLUSION

There was a significant association between the US detected nephritis of the right kidney with decreased renal function, knee pain and knee joint effusion, and significant correlation between depth of knee joint effusion with a degree of knee pain, but there was no significant correlation between dyslipidemia and hepatic steatosis in Balinese women with SLE. Ultrasound might be a help to assess inflammation process of the knee joint in SLE patient, but it was halfway useful to evaluate and correlate with lupus nephritis because of the variable manifestation of renal involvement in SLE patients. To assess the presence of hepatic steatosis, US might be helpful, but further investigation is still needed to explore the pathogenesis of hepatic steatosis with other systemic or hepatic manifestation of SLE.

ACKNOWLEDGEMENT

We thank all of the SLE patients for their participation in this study and thank you to Andi Manaek Hatimbolan, MD and Widyanto Pangarso Adhi, MD, for their assistance in organizing the participants.

DISCLOSURE

No disclosure

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