

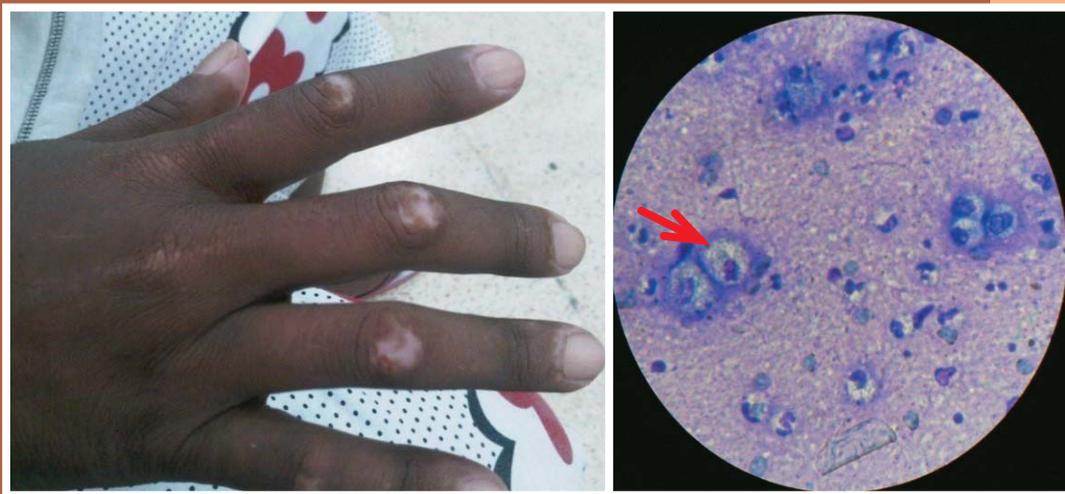
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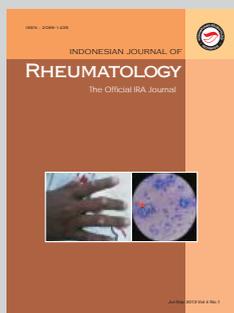


INDONESIAN JOURNAL OF

RHEUMATOLOGY

The Official IRA Journal





Cover image: Sclerodactyly in patient with RA and systemic sclerosis (left; see page 32) and histopathological skin specimen showing histiocytes (right; see page 38) of a patient with multicentric reticulohistiocytosis.

AIMS AND SCOPE

Indonesian Journal of Rheumatology is self-focused on rheumatic diseases and connective tissue disorders in forms of original articles (extended or concise reports), review articles, editorial, letters, leaders, lesson from a 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

Currently there is no national guideline on diagnosis and management of gouty arthritis, so the guidelines from various sources such as American Rheumatism Sub Committee on Classification Criteria for Gout, British Society of Rheumatology, or European League against Rheumatism (EULAR) Task for Gout were used instead. This made diagnosis and management methods varied between physicians. With so many guidelines, it is common to be confused on which guidelines to adhere to.

But then came along evidence-based medicine (EBM). With the invention of EBM, physicians had good assurance that their practice will do more good than harm. It is because EBM seeks to assess the strength of the evidence of risks and benefits of treatments and diagnostic tests.¹ Through the practice of EBM, decision making will no longer be based on others' experiences but rather on an objective evidence of its risks and benefits.

With current advanced technology, physicians are asked to keep their vigilances for life-long study instead, since new evidences in practicing are published in a quick manner and it can definitely change the way of medicine. Hence it is important for doctors to learn about EBM and apply it in their daily practice.

Unfortunately, there are also doctors with no affinity to EBM, such as those involved in the study done by Il Hidayat et al.² They studied a group of general practitioners in regard of their approach in diagnosing and managing gouty arthritis. Using a set of questionnaire, they gathered these practitioners' opinions in gouty arthritis. The result was quite shocking, because the majority of those doctors did not apply evidence-based medicine in their practice nor did they use gold standard tool for diagnosing gouty arthritis. This could lead to mistreatment, since joint pain and hyperuricemia doesn't always mean gout. There were other causes for joint pain such as osteoarthritis, rheumatoid arthritis, osteomyelitis, and a lot of other diseases.

Aside from Gouty arthritis, IJR also features another original article on joint diseases about the correlation of interleukin-6 and disease activity with bone-resorption in premenopausal RA patients by N Akil et al.³ We also have a case report about the sign of erosive polyarthritis that was similar with RA in patients with multicentric reticulohistiocytes written by BPP Suryana et al.⁴

There are other original articles of important topics covered in this journal, such as an article about the effect of disease duration of SLE on peripheral arterial disease by M Merlyn et al, the prevalence and risk factors of vitamin D deficiency in SLE by Y Pangestu et al, and low bone density in hemophilia written by S Anggoro et al.^{5,6,7}

And finally, do not forget to read the case report about the rare condition of a pregnant woman who had systemic sclerosis and hyperthyroid written by Awalia et al.⁸

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Prevalence and factors associated with vitamin D deficiency in systemic lupus erythematosus patients

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ABSTRACT

Background: In addition to the calcium-phosphorus metabolism, vitamin D might also play a role in the immune system. Studies have showed lower levels of vitamin D among SLE patients compared with controls. Researches regarding vitamin D in SLE patients have only been conducted in four seasons' countries (Caucasians subjects in a large part), but no data has been available in tropical countries, particularly Indonesia. The presence of VDR gene polymorphism in different populations will affect the role of vitamin D in the immune system.

Objectives: To determine the prevalence of vitamin D deficiency and identify its risk factors such as lack of sunlight exposure, sunscreen usage, long-term corticosteroid therapy, disease activity, insufficient vitamin D supplementation, and obesity in SLE patients with vitamin D deficiency.

Methods: A cross-sectional study was conducted on SLE patients who were under treatment at Cipto Mangunkusumo General Hospital or members of Indonesian Lupus Foundation. Then those patients completed questionnaires and their 25(OH)D serum levels were measured. The cut-off value of 25(OH)D levels for vitamin D inadequacy is 75 nmol/L, which then grouped into vitamin D insufficiency (25(OH)D 25 - < 75 nmol/L) and vitamin D deficiency (25(OH)D < 25 nmol/L). SLE activity was assessed with MEX-SLEDAI.

Results: During May-June 2008, 80 SLE patients were enrolled with 96.3% female subjects, median age of 26 years (range 17-56 years), 66.3% non-obese, 93.8% using steroid, 62.5% with active disease, and 63.8% have adequate sun exposure. In addition, 81.5% did not use sunscreen and 83.8% did not take vitamin D supplementation. All patients had vitamin D inadequacy with 41.2% in insufficiency level and the other 58.8% in deficiency level. The median of 25 (OH)D levels were 21.85 nmol/L (range 11.5-57.7 nmol/L). It also has been found that vitamin D deficiency occurred more in subjects who were obese, used sunscreens, had lower exposure to sunlight, in a long-term high-dose steroid therapy, had active SLE disease, and had no vitamin D supplements.

Conclusions: All SLE patients had vitamin D inadequacy. Vitamin D deficiency occurred more in subjects who were obese, used sunscreens, had lower exposure to sunlight, in a long-term high-dose steroid therapy, had active SLE disease, and had no vitamin D supplements.

Vitamin D has been known to be involved in calcium and phosphorus metabolism, but it also has roles in the immunity system.¹⁻¹⁰ Most studies stated that the immune system, particularly the T cell response, is controlled by 1.25-(OH)-D₃. Without 1.25-(OH)-D₃, the immune response that is mediated by T cell will not be effective.^{5,10} Besides T cell suppression, 1.25-(OH)-D₃ is also involved in the determination of cytokine secretion system, induction T cell regulations, stimulation of proliferation, and apoptosis.^{6,11} Adequate concentration of vitamin D will improve functions of T-helper cells, dendritic cells, and macrophages.^{6,10,12} In B cells, vitamin D may inhibit antibody secretion and autoantibody formation. It is been known that immunologic factors also plays an important role in SLE (Systemic Lupus Erythematosus) besides genetic, hormonal, and environment factors.¹⁻⁴

Studies linking Vitamin D deficiency with immunology in SLE were generally conducted in animals and concluded that taking vitamin D decreased SLE symptoms and increased survival rate after.^{9, 13-21} Studies in SLE patients had shown that there were lower concentration of vitamin D in patients compared with control group.²²⁻²⁷ Other studies implied low concentration of vitamin D was associated with severeness of disease activities.

Although the benefit effects of vitamin D for SLE patients has been known, the prevalence shows that vitamin D deficiency was mainly caused by the lack of sun exposure, long term steroid therapy, and low vitamin D consumption. Sun exposure is the main source of vitamin D activation and can provide 90% of the body's requirement of vitamin D, but it is also can worsen SLE so the patients are advised to avoid it.¹⁻⁴

Furthermore, vitamin D receptor gene polymorphism found in different population could influence role of vitamin D in the immune system hence influencing SLE disease activities. Recently, studies regarding vitamin D and SLE have been conducted in four seasons' countries with most subjects being Caucasian, but no available data about the prevalence of vitamin D deficiency and SLE in tropical countries, particularly Indonesia. This study aimed to know the prevalence and associated factors of Vitamin D deficiency in SLE patients.

METHODS

Study Design and Patients

This was a cross-sectional study conducted in Cipto Mangunkusumo Hospital, Jakarta and Indonesian Lupus Foundation between May and June 2008. Samples were collected using consecutive method. The inclusion criteria were SLE patients diagnosed according to 1982 American College of Rheumatology Revised Criteria for SLE. Exclusion criteria were patients with chronic kidney disease and liver function disturbance, alcohol ingestion, any conditions related to fat malabsorption (pancreatitis, intestine resection, Crohn's disease), pregnancy, and breastfeeding. All patients were asked to give informed consent. To obtain necessary data, we performed complete anamnesis and questionnaires filling, physical examinations, and laboratory tests (complete blood count, serum creatinine, urinalysis, 24-hour quantitative urine protein, and 25(OH)D serum concentration).

Analytical Statistics

Data obtained were processed electronically using SPSS 10.0 to produce frequency and contingency tables based on the purpose of study. Mean and standard deviation (SD) is used for quantitative data with normal deviation while median and range are used for data with abnormal deviation.

Assessment

A total of 80 SLE patients were included in this study, characteristics of subjects were collected from questionnaires including gender, education, ethnic, participation in Indonesian Lupus Foundation, history of sunscreen usage, duration of sun exposure, steroid dosage per day, other immunosuppressive drugs, and vitamin D consumption. Disease activity were assessed in score based on MAX-SLEDAI.

Currently there is no agreement for the definition of Vitamin D deficiency. Most scientists define vitamin D deficiency as concentration of 25(OH)D < 20 ng/mL (50 nmol/L), relative insufficiencies as concentration of 25(OH)D ranging 21-29 ng/mL, and adequate levels of vitamin D as concentration of 25(OH)D \geq 30 ng/mL. Other opinions define vitamin D inadequacy as concentration of 25(OH)D < 30 ng/mL (75 nmol/L), vitamin D insufficiency as the concentration of 25(OH)D 10 - < 30 ng/mL (25 - < 75 nmol/L), and vitamin D deficiency as concentration of 25(OH)D < 10 ng/mL (25 nmol/L).^{12, 28} This study defined adequate as concentration of 25(OH)D > 30 ng/mL (75 nmol/L) and inadequate as concentration of 25(OH)D < 30 ng/mL (75 nmol/L).

RESULTS

Most subjects were women (96.3%) with a median age of 26 years old (range 17-56 years old). The median duration of illness was 28 months (range 0-216 months). Description of other data can be seen in the Table 1 and Table 2.

Table 1 Characteristics of patients

Characteristic	N	%
Gender		
Male	3	3,8
Female	77	96,3
Education		
Elementary school	3	3,8
Junior high school	6	7,5
Senior high school	41	51,3
College	30	37,5
Member of LFI		
Yes	18	22,5
No	62	77,5
Ethnicity		
Java	57	71,3
Sumatera	21	26,4
Sulawesi	1	1,3
Kalimantan	1	1,3
Protection Utilization History		
Sunscreen	7	8,8
Umbrella	7	8,8
Hijab (hood)	22	27,5
Hat	4	5,0
\geq 2 protectors	25	31,4
No protector	15	18,8
Sunlight exposure sufficiency		
Inadequate	29	36,3
Adequate	51	63,8
Steroid therapy (dosage per day)		
Prednisone 15 mg/day or more	36	45,0
Prednisone less than 15 mg/day	39	48,8
Without steroid	5	6,3
Immunosuppressive therapy (exclude steroid)		
Yes	36	45,0
No	44	55,0
SLE Disease Activity (MEX-SLEDAI)		
Score < 2 (inactive)	30	37,5
Score \geq 2 (active)	50	62,5
Vitamin D Intake (minimal 8 weeks)		
No (<400 IU/day)	72	90
Yes (\geq 400 IU/day)	8	10
Body Mass Index		
Underweight	10	12,5
Normal	27	33,8
Overweight	16	20,0
Obese	27	33,8

Table 2 Distribution of subjects characteristic based on mean, median, standard deviation, and range (minimal and maximal)

Characteristic	Mean	Median	Standard Deviation (SD)	Range	
				Minimal	Maximal
Age (years)*		26		17	56
BMI	23,40		4,62		
Duration of illness (months)*		28		0	216
Steroid dosage per day (mg)*		10		0	250
MEX-SLEDAI*		3,5		0	14
Vitamin D concentration (nmol/L)*		21,85		11,5	57,7

* Abnormal distribution

Prevalence of Vitamin D Deficiencies in SLE Patients

It was found that all subjects had vitamin D inadequacy, in which 33 subjects (41,2%) had vitamin D insufficiency and 27 subjects (58,8%) had vitamin D deficiency. The 25(OH)D median is 21,85nmol/L (range 11,5 – 57,7 nmol/L) (table 3).

Table 3 Prevalence of vitamin D deficiency in SLE Patients

Vitamin D Concentration	Category	N	%
≥75 nmol/L	Adequate	0	0
25 - <75 nmol/L	Insufficient	33	41,2
<25 nmol/L	Deficient	47	58,8

Factors Affecting Vitamin D Deficiencies in SLE Patients

Vitamin D deficiency occurred more frequently in subjects who used sunscreens compared with those who did not. Details of factors influencing vitamin d deficiency in SLE patients can be viewed in Table 4.

Table 4 Factors affecting Vitamin D Deficiency in SLE Patients

Variable		Deficiency		Insufficiencies	
		N	%	N	%
Sunscreens	- Yes	40	61,5	25	38,5
	- No	7	46,7	8	53,3
Exposure to sunlight	- Inadequate	20	69	9	31
	- Adequate	27	52,9	24	47,1
Steroid therapy	- Prednisone 15 mg/day or more	23	63,9	13	36,1
	- Prednisone less than 15 mg/day or no steroid	24	54,5	20	45,4
SLE disease activity (MEX-SLEDAI)	- Active	33	66	17	34
	- Inactive	14	46,7	16	53,3
Vitamin D intake	- No	43	59,7	29	40,3
	- Yes	4	50	4	50
BMI	- Obese	17	63	10	37
	- Non Obese	30	56,6	23	43,4
	- Overweight	12	75	4	25
	- Underweight + normal	18	48,6	19	51,4

Further investigation shows the median of Vitamin D concentration were lower in patients who were obese, used sunscreens, had lower exposure to sunlight, had steroid therapy more than 15 mg per day, had an active SLE disease, and did not have vitamin D supplementation. For more details refer to Table 5.

Table 5 The difference in vitamin D concentration median of factors that affect vitamin D deficiency in SLE patients

Factors that affect vitamin D deficiency in SLE patients	Vit D median and concentration range (nmol/L)	
Sunscreens	- Yes	21,1 (13,4-57,7)
	- No	28,4 (11,5-54,5)
Sunlight exposure sufficient	- Adequate	23,6 (15,7-57,7)
	- Less	19,7 (11,5-54,5)
Steroid therapy	- Prednisone equivalent ≥15 mg/day	21,1 (11,5-57,7)
	- Prednisone equivalent <15 mg/day or no steroid	23,4 (13,4-54,5)
SLE disease activity (MEX-SLEDAI)	- Active	19,7 (11,5-54,8)
	- inactive	25,6 (13,4-57,7)
Vit D intake	- Yes	22,1 (14,6-54,8)
	- No	21,9 (11,5-57,7)
BMI group	- Obese	19,4 (15,4-54,4)
	- Non-obese	23,6 (11,5-57,7)

DISCUSSIONS

There was an interesting finding in which most of the subjects had enough exposure to sunlight even though they knew that it may cause disease recurrence and should be avoided. They felt safe by using protections, such as sunscreen, umbrellas, hoods, hats, or others. This meant most patients understood the importance of avoiding sun exposure to prevent recurrence. This attitude may be supported by sufficient level of education. However, awareness towards the importance of vitamin D consumption was majorly low, which showed lack of knowledge regarding the significance of vitamin D intake in SLE, especially since they need to avoid a direct exposure to sunlight.

A study by Huisman et al²⁶ about vitamin D concentration in women with SLE and fibromyalgia suggested that most of them were suffering from vitamin D deficiency (25(OH)D < 50 nmol/L) with the average concentration of 25 (OH)D 46.5 nmol/L.²⁶ A study by Muller et al²⁹ which assessed vitamin D3 in patients with inflammation diseases (SLE, Rheumatoid Arthritis and Osteoarthritis), found that the 25(OH)D concentrations in SLE patients were significantly different compared with controls and RA patients, with the median 25(OH)D concentration of 13 ng/mL or 32.5 nmol/L.

Another study by Kamen et al³⁰ which measured the concentration of vitamin D in newly-diagnosed SLE patients found that most of them had 25(OH)D concentration of less than 30 ng/mL. Kamen et al³⁰ also analyzed the concentration of vitamin D in 200 SLE patients from various ethnicities and found that the concentrations of vitamin D in African-American and Hispanic races were statistically lower than those of Caucasians and Asians. The concentration of vitamin D in African-American race was 15.5 ng/mL \pm 9.4 while the Caucasian race had 31.3 ng/mL \pm 4.9.

A study by Irastorza et al²⁸ found that the prevalence of vitamin D deficiency was lower than this study, although most of the subjects suffered from vitamin D insufficiency (25(OH)D < 75 nmol/L). There were differences in their characteristics, such as younger age, shorter duration of disease, higher prednisone dosage, and lower vitamin D intake compared with Irastorza's study.

Sheng et al²⁵ found that the concentration of 25(OH)D was significantly lower than the control with mean concentration of 11.5 ng/mL (28.75 nmol/L) \pm 1.5 ng/mL. This study also suggested no correlation found between 25(OH)D concentration and clinical parameters of SLE, disease activities, or steroid consumption. The subjects of this study were younger, had shorter disease duration, and lower steroid consumption. Regarding disease activity, this study was similar with Sheng's study.

The difference of vitamin D concentration between SLE patients in Indonesia and the ones in western countries may be related to their race in addition to inadequate intake of vitamin D. The correlation between race and vitamin D concentration was supported by Muller et al²⁹ who analyzed 25D concentrations in SLE patients from different ethnicities (African-American, Hispanic, Caucasian, and Asian). The study found that concentrations of 25D in African-American and Hispanic patients were significantly lower than those

of Caucasians and Asians. Huisman et al²⁶ found that SLE patients who had no vitamin D supplementation also had lower vitamin D concentration compared with the ones who did.

Further inspection of the factors affecting vitamin D deficiency using median concentration found lower concentration of vitamin D occurred in patients who were obese, used sunscreens, had lower exposure to sunlight, 15 mg/day or more prednisone therapy, active SLE disease, and no vitamin D supplementation.

Another thing that needs attention is the lack of research and definition of vitamin D deficiency, especially in Indonesian younger population. The 25 nmol/L parameter that was used in this study was based on a study on SLE patients in Spain.²⁸ The geographical condition that allowed a lot of exposure to sunlight or low consumption of vitamin D in Indonesia would affect the parameter in defining vitamin D deficiency.

In this study, we know that all SLE patients had vitamin D inadequacy, so they needed vitamin D. Sunlight exposure is the main source of vitamin D for the majority of people, but SLE patients have to avoid sunlight so they get vitamin D from various food sources such as fatty fish (salmon, sardines, mackerel, tuna), fortified cereal, fortified milk, eggs, and cheese.

CONCLUSION

All SLE patients in this study suffered from vitamin D inadequacy and it happened more often in patients who were obese, used sunscreens, and had lower sunlight exposure, high dose steroid, active SLE, and no vitamin D supplementation.

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The effect of disease duration on the incidence of peripheral arterial disease in young adults with systemic lupus erythematosus

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ABSTRACT

Background: Peripheral arterial disease is a chronic complication that affects morbidity and mortality in SLE patient. However, there were only a few of researches studying the relationship of disease duration and peripheral arterial disease event overseas and it has never been studied in Indonesia.

Objectives: To obtain information about the increased event of peripheral arterial disease in women of 40 years old or younger with SLE's duration of five years or longer compared with less than five years.

Methods: This was a case control study conducted between June - August 2012 at Cipto Mangunkusumo hospital, Jakarta. Subjects were women of 40 years old or younger with SLE who visited Rheumatology and Allergy-Immunology outpatient clinic. They were assigned to case and control groups and traced retrospectively using interview and medical record. The relationship between disease duration and peripheral arterial disease was estimated using OR and the role of confounding factors was analysed using logistic regression one by one, resulted in fully adjusted OR.

Results: A total of 90 subjects were recruited, 18 subjects in case group and 72 subjects in control group. Traditional risk factors were similiar in both groups. In multivariat analysis, there was a relationship between disease duration 5 years or longer and peripheral arterial disease with fully adjusted OR 1,9 (95%CI 0,575-6,543). Older age and steroid therapy were the confounding factors.

Conclusion: There was an increased event of peripheral arterial disease in women of 40 years old or younger with SLE's duration five years or longer compared with subjects having the disease duration less than five years, but this increase was not statistically significant.

Keywords: Peripheral arterial disease, lupus erythematosus systemic, disease duration

The fast development of medical technology affects the life expectancy of people with SLE.¹ But this increase of life expectancy brings new challenges as the patients will have complications associated with the accumulation of chronic damage on organs. Without early detection and prompt treatment, there will be decreased quality of life with increased morbidity and mortality. One of

these potential chronic damages is vascular damage caused by early atherosclerosis. According Urowitz et al (1976), the distribution of death causes in SLE was bimodal where the early death was caused by the disease severity or infection, while the late cause was cardiovascular reasons.² Young women with SLE have five times more risk for a cardiovascular event compared with normal control on the same age. This risk increases with age, disease duration, hypertension, dyslipidemia, body mass index, and CRP.^{3,4} In a cohort study on 78 SLE patients without atherosclerosis signs, after five years there were increased thickness on 28% patients and atherosclerotic plaque on 17% patients.⁵ Traditional risk factors could not explain the early pathogenesis of atherosclerosis in SLE, so it was postulated that autoimmune processes causing chronic inflammation was the main contributor.^{6,7} Vascular complications in SLE should have enough attention because the process happens even before symptoms could appear.⁸ Peripheral arterial disease (PAD) is one example of these vascular complications. PAD usually asymptomatic and does not have classical symptoms that it hinders early diagnosis.⁹ It became the cause of decreased quality of life in more than two millions of patients in USA, which affected morbidity, mortality, and increased health spending.¹⁰ SLE patients (mean age 39 years old) were reported having prevalence of abnormal ankle-brachial index (ABI) higher than normal population (37% vs 4%)¹¹ The effect of disease duration on the increasing event of PAD in SLE patients have not been studied enough. A few of studies overseas such as Burgos et al (LUMINA, 2009)¹² in USA, Bhatt et al (2007)¹³ in India, and Wang et al (1993)¹⁴ in China did not give adequate explanation on the relationship between the duration of SLE and this complication. In Indonesia, Sari RM (2009) did a study measuring the thickness of medial intima in the carotid artery of women younger than 40 years old with SLE. The study reported the prevalence of atherosclerosis about 40%, with duration of disease, age, and duration of steroid therapy were the factors with positive correlation.¹⁵ Compared with USG, ABI was cheaper and easier for screening because of its good sensitivity and specificity.¹⁶

METHODS

Study design and subjects

This study was done in Rheumatology and Allergy-Immunology outpatient clinic in Cipto Mangunkusumo Hospital Jakarta between June-August 2012. The samples were taken consecutively and there were 104 subjects eligible for the study, which means they were SLE patients (diagnosis according to the revised ACR criteria in 1997) and younger than 40 years old. 14 subjects were excluded because 8 of them had mixed connective tissue disease, 5 refused to be included in the study, and the other was in her 26 weeks of pregnancy. After interview, medical record tracking, and physical examination, these 90 subjects had their ankle brachial index measured using ABI osilometry by one examiner in Endocrine and Metabolic outpatient clinic in Cipto Mangunkusumo Hospital. Subjects with ABI 0.9 or lower and more than 1.3 were put in the case group (peripheral arterial disease) and those with ABI of 0.9-1.3 were put in the control group.

All of the subjects were interviewed using the same questionnaire. The duration of disease was determined using the data from interview and medical records. Disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Any history of hypertension, DM, dyslipidemia, organs involvement, and therapy was taken from interview and medical records. Subjects with essential hypertension and DM before diagnosis of SLE were excluded.

Data analysis

Data analysis was done with SPSS ver. 16.0.0., using p-value less than 0.05 and CI of 95%. The relation of disease duration with PAD incidence was estimated in OR. Multivariate analysis were done using regression logistic resulted in fully adjusted OR, which was the value after analyzing the confounding factors.

RESULTS

Subjects characteristics

During the study period, there were 104 patients who came to Rheumatology and Allergy-Immunology outpatient clinic eligible for study subjects, but 14 patients were excluded leaving 90 subjects. 18 subjects were put into the case group and 72 subjects were put into the control group. The study was terminated before it had enough samples because there were not enough patients and limited time period. To expand the number of samples, the authors tried national registry of lupus patients, but a lot of the data were invalid.

Table 1 shows the characteristics of study subjects. The mean age was similar in both groups, which was 29.8 years old in the case group and 29 years old in the control group. Subjects in the case group had longer mean duration of disease than control group.

Table 1. Subjects characteristics

Characteristics	Case (n=18)	Control (n=72)	p Value
Mean age (years), SD	28.83 (8.20)	29 (6.62)	--
Duration of disease (months), SD	57 (3-178)	44.5 (1-260)	0.79
Mean BMI (SD)	22.1 (3.74)	21.5 (2.95)	--
Hypertension (%)	1 (5.6%)	3 (4.2%)	0.80
Diabetes Mellitus (%)	0	2 (2.7%)	0.48
Dyslipidemia	7 (38.9)	23 (31.39)	--
Kidney involvement	9 (50%)	28 (38.8%)	0.39
Mean disease activity score (SD)*	4.4 (3.05)	4 (3.68)	--
Chloroquine therapy	8 (44.4%)	20 (27.8%)	0.28
Steroid therapy	17 (94.4%)	71 (98.6%)	--
Mean duration of steroid therapy (months), SD	55.7 (41.17)	43 (45.21)	0.68

*disease activity score was assessed using Mex-Sledai, SD = Standard deviation,

Subjects in the case group had longer mean duration of disease than the control group. Both BMI and disease activity score in the two groups were similar. Traditional risk factors for atherosclerosis such as diabetes, hypertension, and dyslipidemia were also similar in both groups. There was no history of smoking and previous cardiovascular events in the groups. Kidney involvement happened more in the case group than control group. There were 2 subjects with diabetes mellitus in the control group, and it was because of steroid therapy. Chloroquin was more frequently used in case group while steroid was used by a lot of subjects in both groups.

The effect of disease duration on the incidence of peripheral arterial disease

Table 5.2 shows increased risk of PAD in subjects with duration of disease ≥ 5 but this increase is not significant statistically (*crude OR* 1,6 (CI 95% 0,559-4,576); $p=0,38$). This relation did not change after adding confounding factors such as chloroquine therapy, age, steroid therapy, proteinuria, disease activity score, dyslipidemia, and hypertension using logistic regression. The final result was fully adjusted OR 1.9 (CI 95% 0,575-6,543).

Table 2. Multivariate analysis of disease duration and its effect on PAD incidence after including confounding factors.

Variable	OR	CI 95%	P
Duration of disease			
Crude OR	1.6	0.559-4.576	0.38
Adjusted OR			
Chloroquine	1.5	0.511-4.348	0.46
Age	1.9	0.589-5.852	0.29
Steroid therapy	2.1	0.643-6.914	0.21
Proteinuria	1.9	0.595-6.557	0.26
Disease activity score	1.9	0.569-6.387	0.29
dyslipidemia	1.9	0.575-6.512	0.28
Hypertension (fully adjusted)	1.9	0.575-6.543	0.28

DISCUSSION

Demographic characteristics

In this study, the mean age on the case group was 28.83 years old (SD 8,2) and 29 years old on the control group (SD 6,62). The mean age in this study did not differ far from other studies such as Bhatt et al (2007) in India with mean age of 30.7 (SD 8,7).¹³ But there were studies with older mean age, such as LUMINA (2009), a study with multiethnic samples in USA with mean age of 36,5 years old, while Liu et al (2009) in China reported mean age around 33,1 years old (SD 11,8).^{12,17} Cardiovascular incidence in women without SLE were more common after 55 years old, but the same principle did not happen with the SLE group. Manzi et al did an epidemiologic study and reported that women with SLE between 35-44 years old had 5 times risk of cardiovascular incidence compared with the same age group without SLE.³ Most of the subjects on both groups were jobless or housewives with moderate level of education (highschool). This affected their social economic status and their view about SLE. Most of the subjects had insurance so program such as routine examination, laboratory workups, and treatment choice depended on their insurance cover. Besides, a lot of patients lived outside Jakarta, or when they lived in Jakarta, they were far from the hospital. These affected their compliance for routine control or following treatment program.

Clinical characteristics

The subjects in case group tended to had longer duration of disease (57 months) compared with those in the control group (44.5 months). McDonald did a study in USA and Liu did too in China, they both reported longer duration of disease (112 months and 99 months).^{12,17} But Bhatt in India reported shorter duration of disease with 49.4 months.¹³ This variation was most probably caused difference in ethnicity and treatment. Traditional risk factors of atherosclerosis in both groups were similar. This finding was in accordance with previous studies. These traditional risk factors could not specifically explain the pathogenesis of early atherosclerosis in SLE and were not the primary causes.^{18,19}

Subjects in the case group had more kidney involvement. Proteinuria is one of many factors causing early atherosclerosis in SLE, because it stimulates apolipoprotein and cholesterol synthesis in liver, resulting in hypercholesterolemia as a risk factor for atherosclerosis.²⁰

Disease activity assessment using Mex-SLEDAI score showed both groups was in their active phase with mean value of 4.4 (SD 3.05) in the case group and mean value of 4 (SD 3.68) in the control group. This was similar with a study by Sari (2009) involving SLE women in Cipto Mangunkusumo Hospital as her subjects. Her study reported disease activity score of 3.¹⁵ High scores of disease activity were probably due to low compliance in treatment. This condition might be caused by low awareness affected by education level, economy level, and living places far from the hospital.

Most of the subjects in both groups had steroid as their main therapy, but one subject in each group did not have steroid. These subjects had mucocutaneous SLE and they were given chloroquine as main treatment. Those with steroid had it for long duration (more than 1 year), but mean duration of steroid therapy in control group was longer (55.7 months, SD 41.17) than in case group (43 months, SD 45.21). Long duration of steroid therapy was probably related to kidney involvement and high disease activity score.

The effect of disease duration on the incidence of PAD

Urowitz et al (1976) was the first to report that the late cause of death in SLE was secondary to cardiovascular disorder. The risk of cardiovascular incidence increased every year according to duration of SLE. Young women with SLE have five times more risk to experience cardiovascular incidence compared with their normal counterparts. This is caused by early atherosclerosis in SLE. Traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesitas, and sedentary life style have important roles in its formation, but a number of studies have proven that even after these risk factors were modified, those with SLE still have higher rate of cardiovascular incidence. Disease duration, high score of disease activity, kidney involvement, steroid therapy, chloroquine therapy, antiphospholipid antibody, and CRP are some factors related to the early atherosclerosis in SLE.² Analysis with logistic regression in this study showed clinically significant relation between the duration of disease with incidence of PAD (OR 1.9, CI 95% 0,559-4,576), but it was not significant statistically ($p=0,37$). This was caused by low number of samples, low power of study (<80%), and wide confidence interval. On the early estimation of samples, we assumed high OR (4), but in reality the OR estimated in the end was far below, and one of the reason the study was not clinically significant. After re-estimation, for power study of 80% the samples needed for both groups were 136 samples each. For the ratio of case : control 1:4, the study needed 85 in case group and 340 in control group.

OR value of 1.9 was clinically significant because the effect of PAD was significant in a patient's morbidity and mortality. four times more likely to die in ten years compared with patients without PAD.²¹

All subjects in case group were asymptomatic PAD with ABI <0.9. Low ABI (<0.9) in asymptomatic patients is related with morbidity and mortality. It also plays a role as biomarker in cardiovascular incidence. Asymptomatic PAD is related to decreased function of lower extremities in women older than 65 years old.²² Asymptomatic PAD is also related to an

increase by 1.4 in total mortality and 1.5 increase of mortality with cardiovascular causes.²³ A systematic review involving 28,679 subjects reported consistent relationship between low ABI (<0.9) with prognosis of cardiovascular incidence. The specificity of low ABI (<0.9) in detecting coronary heart disease, stroke, and mortality caused by cardiovascular incidence were 92.7%, 92.2%, and 87.8% with positive likelihood ratio of 2.53, 2.45, and 5.61.²⁴

The role of confounding variable in the relation between duration of disease and PAD incidence

In multivariate analysis using logistic regression, there were potential confounding variables consisted of age and duration of steroid therapy. These variables became the confounding variable because they changed OR value more than 10%, in which age changed adjusted OR for 24.5% and duration of steroid therapy changed adjusted OR for 13.5%. A few of studies reported the same result where age was a variable affecting PAD incidence in SLE.^{12,17} Age can not be separated from disease duration, because longer disease duration means older age. Unlike patients without SLE, PAD in SLE happens early with increasing risk factors in accordance to the patient's increasing age.

The effect of steroid therapy on cardiovascular incidence in SLE is still controversial. Treatment using steroid is a dilemma. Inadequate treatment leaves room for inflammation as a trigger for early atherosclerosis, but long duration of steroid increases risk of dyslipidemia and hypertension as risk factors of atherosclerosis. Increased prednisone dose up to 10 mg/ day is related to the increase of cholesterol level by 7.5 mg/dl (SE 1.46) and increased mean arterial pressure by 1.1 mmHg.²⁵ McDonald et al reported duration of steroid therapy as a risk factor for PAD in SLE patients ($p < 0.05$) in which case group received steroid for 109 months compared with control group (34 months). The mean daily dosage for case group was 14 mg/ day and 15 mg/ day for control group.²⁶ But Liu et al in their study about risk factors of digital gangrene in SLE patient stated that steroid did not have any role ($p = 0.10$).¹⁷ More than 5 years of steroid therapy is related with calcification on peripheral blood vessel and more severe clinical symptoms of PAD.²⁶ Because steroid effect is still controversial, confirming direct effect of steroid on PAD incidence needs further study.

Study limitation

One of limiting factors in this study was low number of samples, resulting in low power of the study (<80%). Low power made it difficult to gain statistically significant results. Other limiting factors were no measurement of inflammation factors and level of antibody anticardiolipin because of the limited fund and no reference on normal ABI of Indonesian.

Recall bias is a limitation in case control study, but in this study there were medical records to keep track of disease duration. With multivariate analysis, recall bias and confounding bias effects could be minimized. Because there were no data about SLE population (study base), control group recruitment could not represent common population of SLE because they were taken from those coming to the hospital to get treatment, resulting in uncontrolled selection bias.

Study result generalization

In order to apply this study result to a wider population, the validity of this study needs to be assessed. Internal validity I of this study is good because there was no drop out subjects and all subjects had complete data about their risk factors. Internal validity II is not good enough because subjects in the control group were taken from patients who came to the hospital, causing selection bias and low representative power.

CONCLUSION

There was an increase of PAD incidence in SLE women aged ≤ 40 years old with SLE ≥ 5 years compared with < 5 years, but it was not statistically significant.

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A survey on the clinical diagnosis and management of gout among general practitioners in Bandung

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ABSTRACT

Backgrounds: The global prevalence of gout and hyperuricemia is increasing in recent years. As the most visited health care service, it is thus become more important that general practitioners have proper approach in the diagnosis and treatment of patients with gout, in order to prevent complications of the disease as well as adverse effects of inappropriate and improper use of medications.

Objective: To determine whether the practice of general practitioners on the clinical diagnosis and management of gout in Bandung have been appropriate, with the implementation of evidence-based medicine.

Methods: This was a descriptive cross-sectional qualitative study, done by survey using a questionnaire, conducted among general practitioners who attended medical symposia in Bandung from January to March 2011.

Result: There were 173 respondents participating in this survey. Median age of respondents was 33 years (range 23–73 years), with median duration of practice of 7 years (range 0–45 years). The largest proportion of the respondents often suggested measurement of serum uric acid to patients with any joint pain (45.7%), did not recommend synovial fluid examination to patients suspected of having gout (80.8%), usually prescribed allopurinol to patients with asymptomatic hyperuricemia (52.6%), initiated allopurinol therapy during acute gout attack (35.8%), discontinued allopurinol therapy when serum uric acid normalizes (61.8%), and only very rarely gave prophylactic treatment to patients who started allopurinol therapy (43.4%).

Conclusion: The majority of general practitioners had not applied or aware about evidence-based medicine in the diagnosis and management of gouty arthritis.

Gout is an inflammatory disease of the joint that can induce severe pain and is caused by the deposition of monosodium urate crystals.¹ The disease is strongly associated with hyperuricemia, although not all individuals who have hyperuricemia will suffer from gouty arthritis. The prevalence of hyperuricemia and gouty arthritis worldwide has increased in recent years.² In Indonesia, the actual prevalence of hyperuricemia and gouty arthritis is not known. Previous studies found that the prevalence of hyperuricemia reached 18.9% in Desa Sembiran, Bali, 18.2% in Denpasar,^{3–5} but the prevalence of gout only 1.7% in Central Java.⁶

Joint pain is the most common complaint encountered by general practitioners;⁷ therefore, general practitioners have an important role in determining the etiology of the pain and ruling out the differential diagnoses. General practitioners must be able to make a clinical diagnosis of gouty arthritis and decide the appropriate management.⁸ Currently, Indonesia has no guideline for the diagnosis and management of gouty arthritis; so the diagnosis and management of gout arthritis is done according to the experts' opinion, causing differences in the diagnosis and management of gouty arthritis among general practitioners. If not treated properly, gouty arthritis can lead to recurrent attacks, become chronic with tophus formation, and can cause various complications, including disability.⁹

Residents and doctors in Indonesia have not been evenly distributed with most of them are located in Java.^{10–11} Bandung, as one of the major cities in Java, is where many residents and general practitioners live and practices.¹² In this study we aim to determine whether the practice of general practitioners on clinical diagnosis and management of gout in Bandung have been appropriate with evidence-based medicine.

METHODS

This is a descriptive cross-sectional qualitative study which was done by survey using a set of questionnaire. The survey was conducted among general practitioners who attended medical symposia in Bandung from January to March 2011. Questionnaires were distributed to the respondents prior to the commencement of the symposia and retrieved when the symposia is finished or at rest (convenient sampling technique).

The set of questions were adapted from the questionnaire on gout provided by Dr. H Ralph Schumacher, Jr. from the University of Pennsylvania and Dr. N. Schlesinger from the University of Medicine and Dentistry of New Jersey.¹³ The respondents were requested to choose only one best answer among the choices per question. The choices were grouped according to the appropriateness and consistency to concurrent practice opinion in the literature.¹⁴ Questionnaires with more than 3 items left unanswered or items with ≥ 2 answers were excluded from analysis.

The questions were grouped according to relevance of diagnostic procedure, management of arthritis with hyperuricemia, management of acute gout flare, management of recurrent, intercritical, and chronic tophaceous gout, management of gout through diet modification, and management of gout complication. Demographic characteristics of respondents included age, sex, and length of clinical practice.

Results were analyzed using Statistical Package for Social Sciences software version 17.0. Descriptive analyses included mean and standard deviation or median (for continuous numerical outcomes) and percentage/frequency distribution (for categorical data).

RESULT

Characteristics of respondents

Of the 481 questionnaires distributed, 201 (41.2%) were returned, and 173 (36.0%) were available for evaluation. Median age was 33 years (range 23–73 years), with 95 (54.9%) female respondents. Median length of clinical practice was 7 years (0–45 years). Characteristics of the respondents were elaborated in table 1.

Table 1 Characteristics of respondents (N = 173)

Characteristics	n (%)
Gender	
Male	71 (41)
Female	95 (54.9)
Unindicated	7 (4.1)
Age, years	
<30	59 (34.1)
30–39	49 (28.3)
40–49	30 (17.3)
50–59	14 (8.1)
≥60	15 (8.7)
Unindicated	6 (3.5)
Length of clinical practice, years	
<1	15 (8.7)
1–10	54 (31.2)
11–20	30 (17.3)
21–30	14 (8.1)
31–40	4 (2.3)
>40	1 (0.6)
Unindicated	55 (31.8)

Table 2 Respondents' answer to the questionnaire

No.	Questions	Answer	%
1.	<i>How often do you suggest measurement of serum uric acid level to patients with chief complaint of joint pain?</i>	Often Sometimes Very often Rarely	45.7 35.8 11.0 7.5
2.	<i>Do you usually recommend synovial fluid examination to patients with suspected gouty arthritis?</i>	No Yes Did not know Did not answer	80.3 16.9 2.3 0.6
3.	<i>A male patient presents with chief complaint of joint pain experienced for the first time, without signs of inflammation but with mild hyperuricemia. Do you administer allopurinol to this patient?</i>	Yes No Did not answer	56.1 43.4 0.6
4.	<i>If signs of inflammation are present, do you administer allopurinol to the abovementioned patient?</i>	Yes No	53.2 46.8
5.	<i>A patient is experiencing acute joint pain for the first time. The diagnosis of gout has been confirmed. Do you administer allopurinol to this patient?</i>	Yes No Did not answer	56.6 42.2 1.2
6.	<i>What dose of colchicine do you usually administer in acute gout attack?</i>	2 tabs/day for 3 days Until achieving max. dose of 6 tabs/day 1 tab/day for 3 days 3 tabs/day for 3 days Did not answer Every hour until pain is relieved Until abdominal toxicity occurs	19.7 18.5 17.9 15.0 13.9 10.4 4.6
7.	<i>What do you usually suggest the patient to do to the affected joint?</i>	Rest the joint No difference Frequently move the joint Did not answer	52.6 23.1 22.5 1.7
8.	<i>Ice packs can help relieve the pain in acute gout attack.</i>	Yes No Did not know Did not answer	54.9 37.6 5.8 1.7
9.	<i>Whom do you usually prescribe allopurinol to?</i>	Patients with asymptomatic hyperuricemia Patients who have had 1 acute gout attack in 1 year Patients who have had 2–4 acute gout attacks in 1 year Patients who have had >4 acute gout attacks in 1 year	52.6 25.4 19.7 2.3

10. <i>When do you usually initiate allopurinol therapy?</i>	During acute gout attack	35.8
	1–2 weeks after acute gout attack	31.2
	<1 week after acute gout attack	22.0
	>2 weeks after acute gout attack	10.4
	Did not answer	0.6
11. <i>When do you usually discontinue allopurinol therapy?</i>	When serum uric acid normalizes	61.8
	When serum uric acid is less than normal	22.5
	Never	11.0
	After 1 year	4.0
	Did not answer	0.6
12. <i>What is the target serum uric acid level do you usually set in the management of gout?</i>	<7.0 mg/dL	50.9
	<6.0 mg/dL	26.0
	<5.0 mg/dL	20.2
	Did not know	1.7
	Did not answer	1.2
13. <i>When do you usually repeat the measurement of serum uric acid level?</i>	Every 3–6 months	45.7
	Every month	39.9
	Every 2 months	8.7
	Every week	4.0
	Did not answer	1.2
	Every year	0.6
14. <i>When initiating allopurinol therapy, how often do you give prophylactic treatment to prevent acute gout attacks?</i>	Rarely	43.4
	Sometimes	37.6
	Often	17.3
	Very often	1.7
15. <i>What prophylactic drug do you usually administer?</i>	NSAIDs	41.6
	Do not usually give prophylactic treatment	34.7
	Colchicine	11.6
	Others	5.8
	Did not answer	3.5
	Corticosteroid	2.9
16. <i>Prior to reading this questionnaire, are you aware that gout can cause joint contracture?</i>	Yes	94.2
	No	4.6
	Did not know	1.2
17. <i>How do you usually prevent and manage joint contracture in gout patients?</i>	Educate the patient about joint movement	37.6
	Refer to the Dept. of Physical Medicine & Rehabilitation	28.3
	Tightly control serum uric acid level	19.1
	Did not answer	15.0

NSAIDs, nonsteroidal anti-inflammatory drugs.

Opinion of the respondents in the diagnosis of acute gouty arthritis (questions 1 & 2)

The largest proportion of respondents (45.7%) often suggest measurement of serum uric acid level to patients with chief complaint of joint pain. A small number (11.0%) even do this very often. The majority of respondents (80.3%) do not usually recommend synovial fluid examination to patients with suspected gouty arthritis.

Opinion of the respondents in the management of arthritis with hyperuricemia (questions 3 & 4)

Regardless of the presence of any signs of inflammation, more than half of the respondents would prescribe allopurinol to patients with chief complaint of joint pain and hyperuricemia.

Opinion of the respondents in the management of acute gout flare (questions 5–8)

In the management of acute gout flare, the largest proportion of the respondents (56.6%) administer allopurinol to gout patient with history of 1 episode of acute gouty attack. The respondents' answers are varied in the dose of colchicine, the largest three were 2 tabs/day for 3 days (19.7%), until achieving max. dose of 6 tabs/day (18.5%), and 1 tab /day for 3 days (17.9%). The majority of the respondents usually suggested their patients to rest the affected joint (52.6%) and agreed that ice packs can help relieve the pain in acute gout attack (54.9%).

The choice of drugs among general practitioners in the management of acute gouty attack in patients with normal or impaired renal function are presented in figure 1.

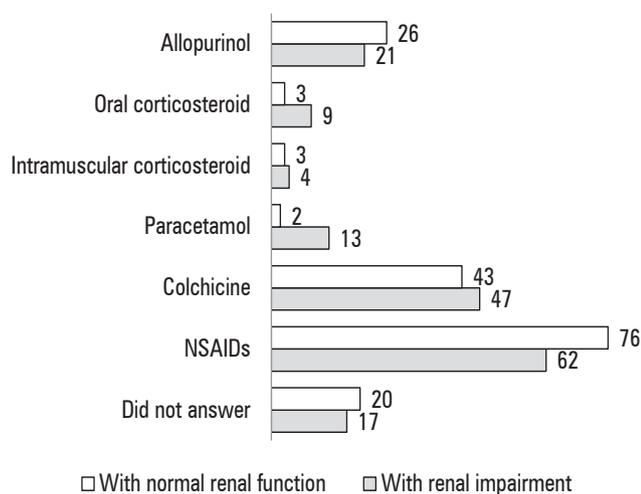


Figure 1 Preferred drugs among the general practitioners in acute gouty attack.

Opinion of the respondents in the management of recurrent, intercritical, and chronic tophaceous gout (questions 9–15)

The largest proportions of the respondents usually prescribe allopurinol to patients with asymptomatic hyperuricemia (52.6%), initiate allopurinol therapy during acute gout attack (35.8%), and discontinue allopurinol therapy when serum uric acid normalizes (61.8%). Most (43.4%) also only rarely administer prophylactic treatment when initiating allopurinol therapy.

Opinion of the respondents in the management of gout through diet modification

The majority of the respondents were aware that meat (beef and lamb), seafood, purine-rich vegetables, and alcohol can increase the risk of gouty arthritis, and that dairy products do not. The result is presented in more detail in figure 2.

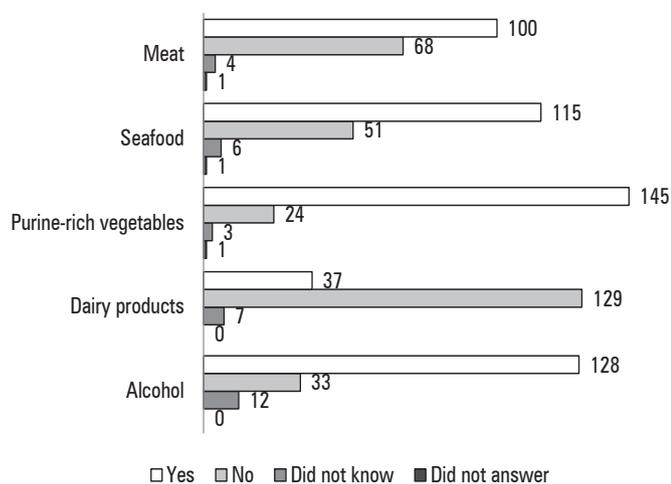


Figure 2 Proportion of the respondents based on their knowledge about the effect of certain diet in increasing the risk of acute gout attack.

Opinion of the respondents in the management of gout complication (questions 16 & 17)

Most of the respondents (94.2%) were aware that gout can cause joint contracture, and the largest proportion (37.6%) usually preferred education about joint movement as a mean to prevent joint contracture in gout patients.

DISCUSSION

There is currently no national guideline for the diagnosis and management of gouty arthritis in Indonesia; thus, guidelines from British Society of Rheumatology (BSR) and European League against Rheumatism (EULAR) Task for Gout, in addition to other recent studies about gout are usually used as guidance for the diagnosis and management of gouty arthritis in Indonesia. Some studies reported that the clinical diagnosis and management of gout is often not consistent with the acceptable practice guidelines available.¹⁴

There is currently a widespread assumption among many Indonesian people that joint pain is always caused by gout, while in truth there are numerous other conditions, such as osteoarthritis, avascular necrosis, crystals, hemarthrosis, joint infection, osteomyelitis, and trauma that can produce joint pain.⁷ Data from the rheumatology outpatient clinic at Hasan Sadikin Hospital in 2010 reported that gouty arthritis accounted for only 3.3% of cases with joint pain; most (72.9%) were found to be caused by osteoarthritis.¹⁵ Patients should be recommended to have their serum uric acid level measured only if the history and physical examination show signs and symptoms of gouty arthritis.⁷ The majority of respondents (56.7%) often, or very often, suggested that patients with chief complaint of joint pain had their serum uric acid level measured. While the gold standard in the diagnosis of gout is the presence of monosodium urate crystals in synovial fluid examined with polarized light microscopy,^{16–17} only 16.8% of the respondents would recommend this to patients with suspected gouty arthritis.

In the management of acute gouty attack in patients with normal renal function, most of the respondents (43.9%) preferred NSAIDs over colchicine (24.9%). Both drugs are acceptable treatment options for acute gout; the choice of drug depends on the physician's preference.^{14,18} Colchicine can be administered at a dose of 0.5 to 0.6 mg orally every hour until joint symptoms eased, the side effects on the digestive system developed, or the maximum dose of 6–8 doses has been reached.^{9,19,20} Recent study recommends that colchicine should be administered at a dose of 0.5 mg, given 2–4 times a day to minimize side effects.¹⁸ This survey showed that more respondents would give colchicine twice a day for 3 days (19.7%) or until the maximum dose of 6 tablets per day had been achieved (18.5%), or once a day for 3 days (17.9%).

In patients with renal impairment, NSAIDs and colchicine should be used with caution. NSAIDs are known to cause acute renal injury while the dosage of colchicine needs to be reduced in patients with renal impairment.^{20–21} The majority of respondents still preferred NSAIDs (35.8%) and colchicine (27.2%) in managing gout in patients with renal impairment.

In an acute attack, the affected joint should be rested, elevated, and exposed in a cool environment.¹⁸ Most of the respondents were already aware of this, by suggesting that the affected joint be rested (52.6%) and placed in a cool environment (54.9%).

Gouty arthritis can be experienced by patients without hyperuricemia and, conversely, patients with hyperuricemia do not always suffer from gouty arthritis.⁹ From the survey we found that more than 50% of the respondents would give allopurinol to patient with hyperuricemia and joint pain experienced for the first time although the diagnosis of gout had not been confirmed.

Allopurinol is the first-line drug for the management of hyperuricemia and gout, and should only be prescribed to hyperuricemic patient with recurrent gout, chronic tophaceous gout, urolithiasis, and urate nephropathy.^{22–24} This survey showed that most of the respondents (52.6%) would give allopurinol to patients with asymptomatic hyperuricemia or after the first gout attack (25.4%). While some studies had shown that hyperuricemia is associated with hypertension, chronic kidney disease, metabolic syndrome, and cardiovascular disease,^{25–28} and induce tophus formation,²³ there is no sufficient evidence which shows that allopurinol administration can greatly reduce the risk of gout attack in general population.¹⁴ Allopurinol is also known to cause digestive disturbance, skin rash, hypersensitivity, and toxic epidermal necrolysis, which may result in death.^{29–30} Some studies suggested that modification of an adverse lifestyle or removal of medicines provoking hyperuricemia will result in no further attacks of gout, while others suggested that 40% patients will not have a further attack within a year, and 7% will have none within 10 years.¹⁸ BSR recommends to initiate allopurinol therapy in patients who have 2 or more gouty attacks in a year.¹⁸ This more selective strategy in the administration of allopurinol can also reduce the cost of therapy.¹⁴ Of all the respondents in this study, only 19.7% would give allopurinol after 2–4 attacks in one year.

Treatment with allopurinol or any attempt to alter serum uric acid level during an acute flare will worsen the inflammatory reaction and prolong the duration of the acute flare;⁹ hence, it is suggested that allopurinol be started 1–2 weeks or more after the resolution of acute gout.¹⁸ This survey showed that 15.0% and 12.1% of the respondents preferred allopurinol as the drug of choice in acute gouty attack in patients with normal renal function and patients with renal impairment, respectively. Although there were more respondents (41.6%) who preferred to start allopurinol therapy at least 1 week after the resolution of acute gout, there were still 35.8% respondents who preferred to give allopurinol during acute attack.

To prevent acute gout attack in patients starting allopurinol therapy, prophylaxis should be administered concurrently. The first-line drug used for prophylaxis is colchicine. In patients who cannot tolerate colchicine, an NSAID can be used but the duration should be limited to 6 weeks. This survey showed

that there were only 1.7% of respondents who very often gave prophylaxis while 43.4% would only rarely did so. From those who usually administered prophylactic treatment, only 11.6% preferred colchicine. Once initiated, allopurinol should be kept lifelong with a dose sufficient to maintain serum uric acid level <5 mg/dL (BSR) or <6 mg/dL (EULAR).^{18,31} The majority of respondents would discontinue allopurinol when serum uric acid normalizes (61.8%) and of respondents set <7 mg/dL as the target serum uric acid level (51.5%). For follow up, BSR suggests to check serum uric acid level three-monthly for the first year and then annually thereafter.¹⁸

Some experts suggest that some restriction of purine intake is helpful in controlling gout and hyperuricemia in many patients, despite the fact that a totally purine-free diet only decreases the mean serum uric acid level by about 1 mg/dL.⁹ For dietary management, patients with gout should avoid red meat, seafood (especially shellfish), and alcohol, while they should increase the intake of low-fat dairy products such as skim milk and low-fat yoghurt.³² More than half of the respondents were aware that meat such as beef and goat (57.8%), seafood (66.5%), and alcohol (74.0%) would increase risk of gout while 74.6% were aware that dairy products would not increase risk of gout. Vegetables such as mushrooms, asparagus, cauliflower, spinach, lentils and soya beans are also rich in purines, but recent studies suggest that vegetarian diets high in purines are associated with lower levels of serum uric acid level and lower risk of gout.³² We found that only 13.9% of respondents were aware about this.

Tophaceous gout can cause joint contracture.³³ This can be prevented by strictly controlling serum uric acid level below 5 or 6 mg/dL.³⁴ Most of the respondents (94.2%) were aware that gout can cause joint contracture but only 19.1% would control serum uric acid level to prevent it.

The questionnaire used in this survey was not designed to determine the level of knowledge of the respondents, but only to assess the opinions of respondents about each question. The various opinions we obtained from the respondents showed that there was still a gap between the result of recent studies and the clinical diagnosis and management of gout applied in health-care centers in Bandung. This may increase the risk of gout patients to develop complications, including a decrease in the quality of life.³⁵ A guideline about the clinical diagnosis and management of gout is needed to improve the quality of healthcare services to patients with gout. Principles of gout management should be socialized to medical students, general practitioners, and specialist who may be treating patients with gout.

CONCLUSION

This survey showed that the majority of general practitioners in Bandung had not applied or aware of the diagnosis and management of gouty arthritis in accordance to evidence-based medicine.

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Correlation of serum level of interleukin-6 and disease activity with bone-resorption activity in premenopausal rheumatoid arthritis patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, systemic disease characterized by inflammation and cellular proliferation in the synovial lining of joints that can ultimately result in cartilage and bone destruction. Patients with RA are at increased risk of osteoporotic fractures in both axial and appendicular bones. Several cytokines are involved in the pathogenesis of osteoporotic RA patients, including tumor necrosis factor α , interleukin (IL)-1, IL-6, and IL-17. Among these cytokines, IL-6 has a pivotal role in the pathogenesis of increased bone resorption in postmenopausal RA patients. There are currently scarce data concerning this process in premenopausal RA patients.

Objective: To determine the correlation of serum level IL-6 and disease activity with bone-resorption activity in premenopausal RA patients.

Methods: This is a cross-sectional study with consecutive sampling method conducted at the Division of Rheumatology, Cipto Mangunkusumo General Hospital from June until August 2010. Bone-resorption activity was quantified using serum C-terminal cross-linking telopeptide of type I collagen (CTX-I) level, while disease activity was assessed using the 28-joint disease activity (DAS28) score. Statistical analysis was performed to investigate the correlation of serum IL-6 level and disease activity with serum CTX-I level.

Results: There were 38 patients enrolled in this study. Mean serum level of IL-6 was 10.99 pg/mL (SD 16.06). Mean serum level of CTX-I was 405.37 pg/mL (SD 199.32). There was no significant correlation ($p = 0.252$) between serum IL-6 level with serum CTX-I level; however, a significant correlation existed ($r = 0.389$, $p = 0.033$) among seropositive patients. There was no significant correlation ($p = 0.257$) between the DAS28 score with serum CTX-I level.

Conclusion: There were no significant correlation either of serum IL-6 level or disease activity with serum CTX-I level among patients in this study.

Rheumatoid arthritis (RA) is a chronic systemic disorder characterized by synovial proliferation and infiltration of inflammatory cells, particularly CD4+ cells, which result in destruction of joint cartilage and bone.^{1,2} Besides joint destruction that can lead to morbidity and disability, which is the primary focus in the management of RA, the

patients also are at increased risk of osteoporotic fracture of the axial as well as appendicular bones.³ Osteoporosis is one of the main comorbidity in RA patients besides infection and cardiovascular disease.⁴ The prevalence of osteoporosis in RA patients ranges between 14.7 and 31.5%. Increase in the prevalence of osteoporosis increases the risk of osteoporotic fracture up to four times.⁵ This condition makes the management of RA more difficult and cause more financial burden.⁶

Several cytokines play role in the pathogenesis of osteoporosis in RA, such as tumor necrosis factor α (TNF α),⁷ interleukin (IL)-1,⁸ IL-6,^{9,10} and IL-17.¹¹ Among those, IL-6 is of important consideration because, firstly, it has a relatively constant serum level;¹² secondly, IL-6 in RA patients has synovial level that correlates with its serum level, which indicates synovial origin of the serum IL-6;¹³ thirdly, local as well as generalized osteoporosis that is commonly found in active RA correlates well with the bone marrow level of IL-6.¹⁴

Kawiyana¹² who conducted a study among estrogen-deficient postmenopausal women in Bali reported that IL-6 level was significantly higher in those with osteoporosis compared with those without osteoporosis. Mamohara et al¹⁵ found an increase in bone-resorption activity in postmenopausal women with active RA. Another study found a significant decrease in bone mass (measured in bone mineral density) in early RA patient and a significant correlation of the decrease with disease activity.¹⁶

Advancement is also showed in the management of RA by the discovery of biologic agents that induce better response than disease-modifying antirheumatic drugs. However, only less than 50% of patients reached American College of Rheumatology (ACR) 50 with anti-TNF α . Other agents such as rituximab and abatacept were effective in some patients that did not show response with anti-TNF α , but they rarely induce remission, and overall 50% improvement was not better than anti-TNF α . IL-6 with its pleiotropic effect, either in the activation of inflammatory response or osteoclastogenesis, has been a target of therapy with tocilizumab, a human antibody against IL-6 receptor, which has entered phase II clinical trial.¹⁷

Inflammation in RA can be assessed by nonspecific laboratory tests such as C-reactive protein (CRP) or erythrocyte sedimentation rate, but the sensitivity or accuracy of these tests are limited in evaluating local erosion in bone or more generalized loss of bone mass. C-terminal cross-linking telopeptide of type I collagen (CTX-I) is one of the more specific marker that can better represent bone-resorption activity in RA. Compared with other bone resorption markers, CTX-I is more specific in showing degradation of collagen type I, which is the main component of bone.¹⁸ Besides bone-resorption activity, serum or urine level of CTX-I is also useful in predicting fracture risk in elderly women. The Epidemiology of Osteoporosis (EPIDOS) study found that women with increased serum or urine CTX-I level above the level observed in premenopausal women have twofold risk of fracture of the proximal femur.¹⁹

PATIENTS AND METHODS

This study was conducted at the Division of Rheumatology at Cipto Mangunkusumo General Hospital from June until August 2010. Sample was collected using consecutive method. The inclusion criteria were premenopausal women who were diagnosed based on the 1987 ACR criteria for RA with the first onset of disease at the age of >16 years old. The exclusion criteria were corticosteroid treatment with a dose equivalent to ≥ 7.5 mg of prednisone per day in the last 1 month; treatment with bisphosphonate drugs, selective estrogen receptor modulators, calcitonin, or in hormone-replacement therapy; presence of signs of acute inflammation; clinical or radiological signs of tuberculosis; history of cigarette smoking or alcohol drinking; body mass index <18.5; and presence of the following conditions: diabetes mellitus, thyrotoxicosis, chronic liver disease, chronic kidney failure, or metastasis to the bone. All patients agreed to participate and signed informed consent. The study was approved by the Ethical Committee of the University of Indonesia School of Medicine.

We asked each patient to fill a questionnaire in order to obtain demographic as well as clinical data and performed physical examinations and blood sample test to obtain necessary data for disease activity and serum IL-6 and CTX-I level.

Disease activity was measured using the 28-joint Disease Activity Score (DAS28)^{20,21} with 4 variables: swollen joint count (SJC, total 28), tender joint count (TJC, total 28), sedimentation rate (SR), and global health assessment using visual analogue scale (VAS) with a scale ranging from 0 to 100.

Measurement of serum IL-6 level was performed using enzyme-linked immunosorbent assay with Quantikine Human IL-6 Immunoassay reagent (R and D System Inc., Minneapolis, USA). Bone resorption activity was measured by quantifying serum CTX-I level using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

The collected data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 16. Correlations of the IL-6 and the CTX-I level with DAS28 were analyzed by Pearson or Spearman test as appropriate. Significance was defined as $p < 0.05$.

RESULTS

Thirty eight patients were enrolled in this study; the mean age was 36.84 years old (SD 8.0) ranging from 19 to 50 years old. Most of the patients were in the 31- to 40-year old age group. The demographic and clinical characteristics of the patients are further elaborated in table 1 while the distribution of the serum IL-6 and CTX-I level among patients are presented in table 2.

Table 1 Characteristics of patients (N = 38)

Characteristics	n (%)*
Age, mean (SD) (range)	36.84 (8.0) (19–50)
≤20 years old	1 (2.6)
21–30 years old	5 (13.2)
31–40 years old	18 (47.4)
41–50 years old	14 (36.8)
Educational level	
Low (none–elementary school)	4 (10.5)
Medium (junior high school–senior high school)	14 (36.8)
High (diploma, bachelor, master degree, or higher)	20 (52.6)
Occupation	
Homemaker	15 (39.5)
Employee	8 (21.1)
Civil servant	6 (15.8)
Others	9 (23.6)
Ethnicity	
Betawi	11 (28.9)
Javanese	10 (26.3)
Padang	7 (18.4)
Others	10 (26.3)
Body mass index, mean (SD)	22.9 (3.6)
Duration of disease, month, mean (SD)	46 (31.77)
DAS28 score, mean (SD)	3.88 (1.28)
Remission	7 (18.4)
Low disease activity	5 (13.2)
Medium disease activity	19 (50)
High disease activity	7 (18.4)
ESR, mm/hr, mean (SD)	37.47 (21.59)
Serologic test (RF or anti-CCP)	
Postive	30 (78.9)
Negative	8 (21.1)
Disease-modifying antirheumatic drugs	
Methotrexate	23 (60.5)
Methotrexate combination therapy	10 (26.3)
Sulfasalazine	4 (10.5)
Sulfasalazine/chloroquine combination	1 (2.6)
Analgesics/NSAIDs	
Paracetamol	1 (3.6)
Nonselective NSAIDs	18 (47.4)
COX-2 selective NSAIDs	5 (13.2)
None	14 (36.8)

*Unless otherwise specified.

DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; NSAIDs, nonsteroidal anti-inflammatory drugs, COX-2, cyclooxygenase-2.

Table 2 Distribution of interleukin-6 (IL-6) and C-terminal cross-linking telopeptide of type I collagen (CTx-I) level among patients

	Mean (SD)	Median (range)
IL-6, pg/mL	10.99 (16.06)	5.29 (1.30–81.66)
CTx-I, pg/mL	405.37 (199.32)	373.50 (78–960)

Correlation between serum CTx-I level and disease activity

From the Pearson's test we found no significant correlation between the DAS28 score and serum CTx-I level ($r = 0.189$, $p = 0.257$). There was also no significant correlation among seropositive patients ($r = 0.335$, $p = 0.071$). Scatter diagram of the correlation between serum CTx-I level and the DAS28 score are presented in figure 1.

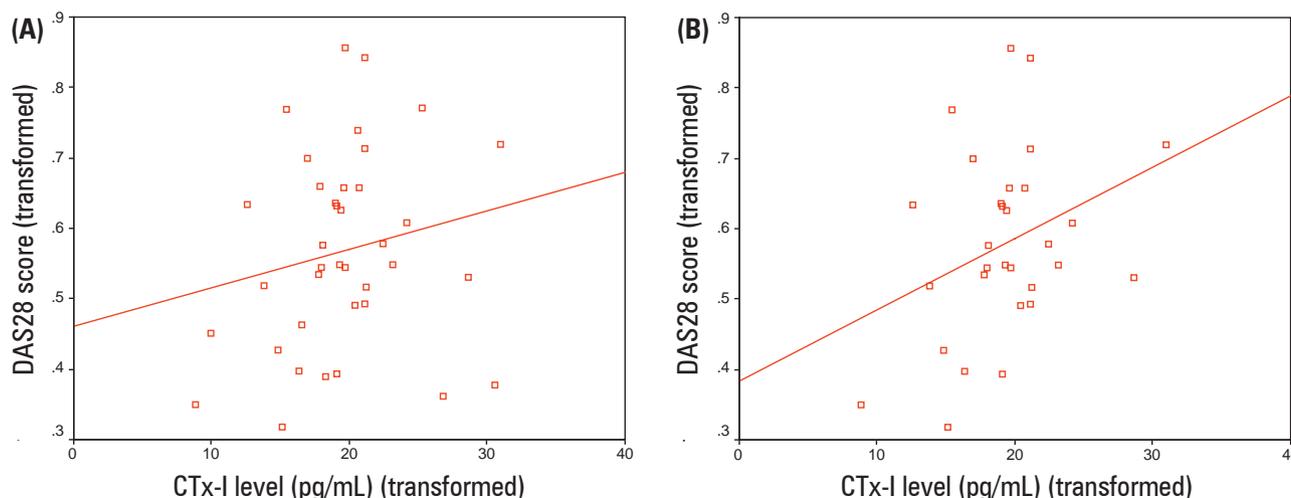


Figure 1 Correlation between serum C-terminal cross-linking telopeptide of type I collagen (CTx-I) level and the 28-joint Disease Activity Score (DAS28) in all patients (A) and in seropositive patients (B). Both analysis showed no significant correlation between the variables ($r = 0.189$, $p = 0.257$ and $r = 0.335$, $p = 0.071$, respectively).

Correlation between serum IL-6 level and disease activity

From the Pearson's test we found no significant correlation between serum IL-6 level and the DAS28 score ($r = 0.190$, $p = 0.252$). However, significant correlation existed among the seropositive patients ($r = 0.389$, $p = 0.033$). Scatter diagram of the correlation between serum IL-6 level and the DAS28 score are presented in figure 2.

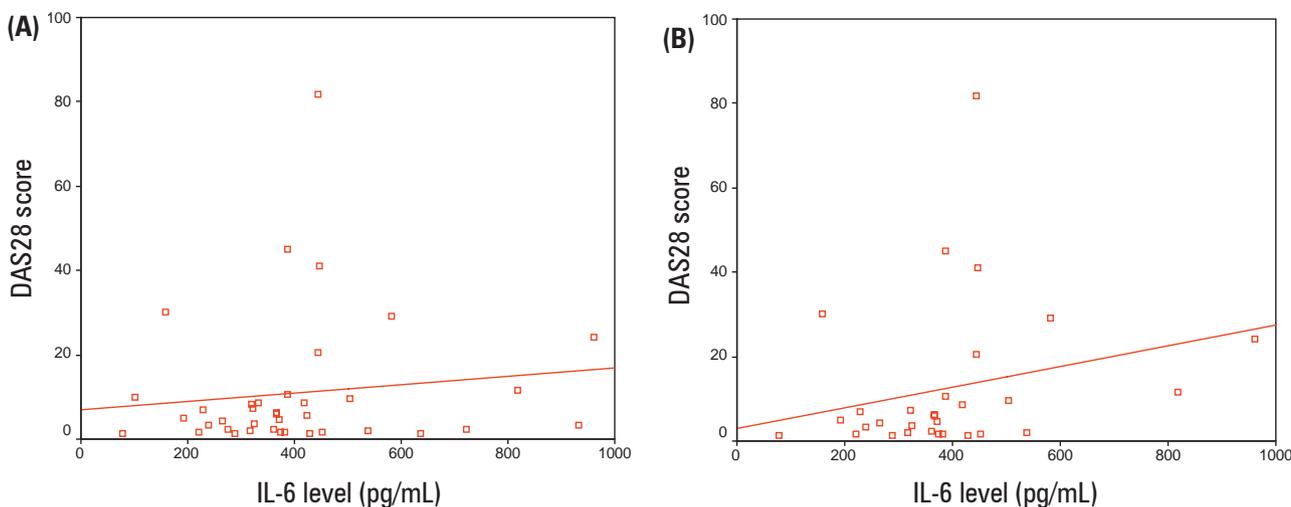


Figure 2 Correlation between serum interleukin-6 (IL-6) level and the 28-joint Disease Activity Score (DAS28) in all patients (A) and in seropositive patients (B). Both analysis showed no significant correlation between the variables ($r = 0.190$, $p = 0.252$ and $r = 0.389$, $p = 0.033$, respectively).

DISCUSSION

Among patients in this study, serum CTx-I level had a mean value of 405.37 with a range of 78–960 pg/mL. This result is higher than a previous study by Wislowska et al²² who found mean CTx-I level of 150 pg/mL with a range of 10–640 pg/mL, although it is important to note that postmenopausal women were also included in that study. The CTx-I level in this study is relatively similar to a 10-year cohort study by Syversen et al²³ who found a mean CTx-I value of 410 pg/mL with a range of 310–750 pg/mL among patients with progressive joint damage and mean CTx-I value of 320 pg/mL with a range of 210–490 pg/mL among patients without progressive joint damage.

Serum IL-6 level in this study had a mean value of 10.99 pg/mL with a range of 1.30–81.66 pg/mL. Previous studies have shown various result of serum IL-6 level in RA patients. A relatively similar result in serum IL-6 level was found in studies by Knudsen et al²⁴ who found a range of 1.8–68 pg/mL, Litinsky et al²⁵ who found a mean value of 16 pg/mL, and Shingada et al²⁶ who found a mean value of 19.814 (SD 11.379) (the latter involved both male and female patients with active RA aged between 38 and 82 years old). A lower value of IL-6 level could be found in a study by Kawiyana et al¹² who study the IL-6 level in estrogen-deficient postmenopausal women with and without osteoporosis; mean values of IL-6 level were 3.47 (SD 1.75) and 2.51 (SD 1.13) in the osteoporosis and non-osteoporosis group, respectively. These data suggest that serum IL-6 level is higher in women with RA regardless of the menstrual status. A higher IL-6 level was found in a study by Robak et al²⁷ with mean IL-6 value of 52.7 pg/mL with a range of 1.5–234 pg/mL.

In this study we found no significant correlation between disease activity and bone resorption activity, both in all patients and in seropositive patients. However, there was a tendency that the seropositive patients, which had more severe disease activity, had higher bone resorption activity. Wislowska et al²² also found no significant correlation between disease activity and serum CTx-I level. This nonsignificant correlation could be caused by several conditions, one of which is that the disease activity as measured by DAS28 do not fully represent systemic inflammation at the time of the study. Van Tuyl et al in his review²⁸ stated that the percentage of remission varied from 9% when using the ACR to 20% when using the DAS28. This means that when using the DAS28, there is a substantial residual disease activity. Other conditions that may affect the result were duration of disease, which correlates with the serum CTx-I level. Wislowska et al²² in their study found that RA patients with disease duration of more than 10 years have significantly lower level of CTx-I than patients with disease duration of less than 10 years, which means that the bone turnover activity are lower with longer duration of disease.

IL-6 is one of the cytokines that have important role in RA-related osteoclastogenesis. Several mechanisms involved in the effect of IL-6 on osteoblast, osteoclast, or cells of the immune system, such as T lymphocyte, macrophage, and fibroblast that in the end increase the expression of receptor activator of nuclear factor- κ B ligand (RANKL) and thus causes proliferation, differentiation, and activation of osteoclast to

perform bone-resorption activity.^{29,30}

Analysis on the samples from 38 patients in this study failed to show statistically significant correlation between serum IL-6 level and serum CTx-I level. As has been stated, there are four types of cytokines that have role in increasing bone-resorption activity in RA. The other cytokines may have more dominant influence on bone-resorption activity, which could explain the result of our study. Studies that involve the other cytokines may improve our understanding of the role of the other cytokines. Moreover, it also possible that yet another cytokine exists that has even more influence on the bone-resorption activity.

The influence of genetic factors on bone-resorption activity is also of important consideration. Ferrari et al³¹ in his study that enrolled postmenopausal healthy women found two polymorphism of the gene that regulate IL-6 expression, which in turn influence the CRP level and bone-resorption activity. Polymorphism of vitamin D receptor is another genetic factor that has been proven to influence the decrease in bone mass in RA patients. Two alleles from the vitamin D receptor gene are associated with systemic decrease in bone mass in RA patients.³²

A significant result was obtained when the analysis was performed on only the seropositive samples. This is in line with previous studies which stated that seropositive RA patients, either RF-positive or anti-CCP-positive, showed more severe disease activity, more joint erosion, and more progressive disease with bone destruction compared with seronegative RA patients.³³ Shingada et al²⁶ in a study that involved 35 active RA patients also found similar result: there was a significant positive correlation ($r = 0.352$, $p = 0.03$) between serum CTx-I level and serum IL-6 level.

The positive correlation of serum IL-6 and CTx-I level in this study also support the possibility of the role of IL-6 in increasing the degradation of type-I collagen because of bone resorption, particularly in premenopausal women with seropositive RA.

There are several limitations that may influence the result of this study and important to consider in the interpretation. First, this study did not control the use of NSAIDs among the patients. NSAIDs use may affect the measurement of DAS28 (while the joint and bone damage remain unaffected). Secondly, patients enrolled in this study had a wide range of duration of disease. In early RA, joint tenderness and swelling is minimal; so the patient will have lower DAS28 score, while degradation of joint cartilage and bone is already in process. In contrast, with longer duration of disease there is a decrease in bone turnover. Thirdly, this study did not evaluate bone formation; therefore, decrease in bone mass among patients in this study may be the result of increased bone resorption or decreased bone formation, or the combination of both processes.

CONCLUSION

Among the premenopausal RA patients in this study, there were no significant correlation of serum IL-6 level and disease activity with bone-resorption activity.

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The characteristics of hemophilic patients with decreased bone density in Cipto Mangunkusumo Hospital Jakarta

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ABSTRACT

Background: Hemophilia can cause musculoskeletal complications and decreased bone density is one of those complications. The profile of hemophilic patients with decreased bone density in Indonesia is still unknown.

Objective: To estimate the proportion of decreased bone density hemophilia and to learn the characteristics of hemophilic patients with decreased bone density.

Methods: This is a cross-sectional study done in June - November 2012. Subjects were adult hemophilic patients from 19-50 years old in Hematology- Oncology outpatient clinic Cipto Mangunkusumo Hospital. Estimated variables were bone density mass, age, body mass index, physical activity, arthropathy, substitution therapy, HIV, and HCV infection.

Result: 63 subjects were included in the study with median age of 26 years old. The proportion of decreased bone density in hemophilia was 6.3%. Subjects with decreased bone density were younger (19 years old vs 26 years old), have lower BMI (18,6 + 2,8 kg/m² vs 21,5 + 3,8 kg/m²), used more substitution therapy (4047 IU/month vs 2000 IU/month), and have better clinical arthropathy score. HCV infection happened on 25% subjects with decreased bone density while HIV was on 1.6% of subjects.

Conclusion: Decreased bone density was found in 6.3% of subjects with hemophilia. They were younger, have lower BMI, better joint score, lower infection caused by transfusion, and more bleeding compared with subjects with normal bone density.

Hemophilia is a disorder of blood coagulation caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). It is linked by mutation in X chromosom and is found in 1 of 10,000 births. Hemophilia A dominates the prevalence with more than 80-85% cases.¹ According to the survey data by World Federation of Hemophilia (WFH) in 105 countries in 2009, there were 150,000 cases of hemophilia.² Complications from hemophilia were caused by the disease itself or because of its treatment. One of the most common complications in hemophilia was musculoskeletal problems, and osteoporosis was a prime example.³

Osteoporosis is a disease characterized by low bone mass and bone structure deterioration causing

fragility and increased risk of fracture.⁴ Those with osteoporosis are commonly at high risk for fracture of pelvis, spine, and lower arms.⁵ Currently, there are 200 millions of people with osteoporosis.⁶ This disease was diagnosed using bone densitometry and measured according to the criteria from WHO with T score for post-menopause women and Z-score for younger people.⁴

Decreased bone density in hemophilia was first reported by Gallacher et al in 1994.⁷ A few studies after reported the same results in adults and children and it was later supported with a meta-analysis study.⁷⁻¹⁴ Because bone density is related with the risk of fracture, hemophilic patients with decreased bone density will have increased risk of fracture.

In hemophilia, fracture is a complex problem because of its morbidity and good hemostasis is needed for perioperative and rehabilitative period.¹ Its management also needs cooperation between hematologists, surgeons, and medical rehabilitationists, besides expensive billing caused by coagulation factor concentrates.¹⁵⁻¹⁷ They are become the main reason of risk factor identification hemophilia to prevent osteoporosis and fracture.

A number of studies about decreased bone density and related factors were done in various countries and regions.^{9,10,14,18,19,20} This studies of osteoporosis in adults with hemophilia reported consistent result about decreased bone density in hemophilic patients compared with their normal counterpart. Unfortunately, these studies used T-score to define osteoporosis in young subjects and their Z-score cut-off points were different from recommendations in guidelines.^{14,18,19} They also had different characteristics compared with Indonesian patients, so those results could not be applied here. Because of those limitations, this study was done to understand the proportion of decreased bone density in hemophilia and the patients' characteristics in Indonesia.

METHODS

This is a cross-sectional study to estimate the proportion of decreased bone density and to learn the patients' characteristics. The study was done from June 2012 – November 2012 in Hematology- Oncology outpatient clinic, Cipto Mangunkusumo Hospital.

Inclusion criteria used was hemophilic patients between 19-50 years old, while exclusion criteria were subjects with prosthesis on the location examination of BMD, antiviral for HIV or HCV, previous or ongoing treatment of osteoporosis (bisphosphonate, SERM, calcitonin, strontium ranelat, hormone replacement therapy); routine steroid for 6 weeks or more, one or more comorbid such as rheumatoid arthritis, SLE, CKD, and patients refusing to be involved in the study.

The variables included in the estimation were age, BMI, hormone replacement therapy, physical activity, clinical arthropathy degree, radiological arthropathy degree, HIV, HCV, bone density measurement, and history of fracture. BMD examination was done with GE Lunar Scan and the results were reported using Z-score. Decreased bone density was defined as Z-score -2 or less. HJHS score was estimated using guidelines according to International Prophylaxis Study Group. Knee radiologic photos were interpreted by a radiologist using Arnold-Hilgartner score. Score of 3 or more was categorized as significant arthropathy.

The data of subject characteristics is presented in tables. Numeric data with normal distribution is presented in mean + standard deviation (SD) while abnormal distribution is presented in median. Categorical data is presented in amount (n) and percentage. Statistic processing was done using SPSS.

RESULTS

Between June – November 2012, a tracing to 152 hemophilic patients living in Jabodetabek listed in Integrated Hemophilia Team was done. Out of 84 patients that were managed to be contacted, 63 of them fulfilled inclusion criteria to be involved in the study. Their characteristics are seen on the table 1.

All subjects in this study were male with median age of 26 years old (19-46 years old) and most of them graduated from high school and university. 53 subjects had hemophilia A while the rest of them had hemophilia B and most of them had severe hemophilia. About 74.6% of subjects had normal BMI and 25.4% had low BMI. 54% subjects had Hepatitis C while HIV was found in 1 subject.

History of fracture was found in 14,3% of subjects. All of them had normal bone density and most of them (90%) were caused by trauma. Median BMD of those subjects was 1,159 g/cm² while the median BMD of subjects without any fracture history was 1,023 g/cm².

Table 1 The characteristics of the subjects in study

Variable	Total (n = 63)
Age (years), median (min-max)	26 (19-46)
Age at diagnosis (month), median (min-max)	9 (1-324)
Duration since diagnosis (month), median (min-max)	268 (60-492)
Education, n (%)	
- Basic (elementary - junior high school)	1 (1,6)
- Middle (senior high school)	49 (77,8)
- Advanced (college or university)	13 (20,6)
Body mass index (kg/m ²), mean + SD	21,4 + 3,8
Type of hemophilia, n (%)	
- Hemophilia A	53 (84,1)
- Hemophilia B	10 (15,9)
Degree of hemophilia severity, n (%)	
- Mild hemophilia	5 (7,9)
- Moderate hemophilia	18 (28,6)
- Severe hemophilia	40 (63,5)

Substitution therapy in the last 1 month	
- Factor VIII (IU), median (min-max)	2000 (0-7350)
- Factor IX (IU), mean + SD	2366,2 + 1443,4
Substitution therapy per kg body weight in the last 1 month	
- Factor VIII (IU/kg), median (min-max)	35,5 (0-126,9)
- Factor IX (IU/kg), mean + SD	39,5 + 27,5
Substitution therapy in the last 3 months	
- Factor VIII (IU), median (min-max)	6000 (0 - 21550)
- Factor IX (IU), mean + SD	5469,7 + 3117,3
Substitution therapy per kg body weight in the last 3 months	
- Factor VIII (IU/kg), median (min-max)	101,1 (0-359,4)
- Factor IX (IU/kg), mean + SD	89,8 + 57,6
BMD (g/cm ²), median (min-max)	1,036 (0,808-1,337)
HCV infection, n (%)	
- Positive	34 (54)
- Negative	29 (46)
HIV infection, n (%)	
- Positive	1 (1,6)
- Negative	62 (98,4)

Table 2 Fracture on hemophilic subjects

Variable	Total (n=63)
History of fracture, n (%)	
- Positive	9 (14,3)
Location of fracture, n*	
- Clavicle	4
- Femur	3
- Tibia	1
- Patella	1
Fibula	1
Cause of fracture, n*	
- Traffic accident	6
- Domestic accident	1
- Nature disaster (earthquake)	1
- Minimal trauma	2
- Negative	54 (85,7)

Proportion of decreased bone mass density was 6.3%. But the results were different when using Z-score and T-score. Bone density characteristics of the subjects can be seen below.

Table 3 Bone density on hemophilia

Variabel	Total subyek (n=63)
BMD (g/cm ²), median (min-max)	1,036 (0,808-1,337)
Decreased bone density according to the ISCD*	
Z-score < -2, n(%)	4 (6,3%)
Z-score > -2, n(%)	59 (93,7%)
osteopenia and osteoporosis according to the WHO**	
Normal (T-score > -1), n (%)	40 (70,2%)
Osteopenia/osteoporosis (T-score < -1), n (%)	17 (29,8%)

*The criteria of decreased bone density according to the ISCD is used for males younger than 50 years old and pre-menopause females using cut-off Z-score < -2
** osteopenia and osteoporosis according to the WHO is used for post-menopause females and males older than 50 years old

All subjects with decreased bone density had hemophilia A, lower BMI, lower incidence of HCV or HIV infection, and younger compared with subjects with normal bone density. There was a significant difference of substitution therapy between subjects with normal and decreased bone density. Subjects with decreased bone density used substitution therapy twice as much as subjects with normal bone density in the last 1 month (median 4047 IU/month vs 2000 IU/month). The same tendency also happened in substitutional therapy

use in the last 3 months (10872,5 IU vs 6632,6 IU).

Both groups had similar level of physical activities. In decreased BMD group, their arthropathy scores were better but the incidence rates of knee arthropathy were similar in both groups. The subjects' characteristics can be seen below.

Table 4 The characteristics of subjects with decreased bone density

Variable	Subjects with decreased bone density (n=4)	Subjects with normal bone density (n=59)
Age (years), median (min-max)	19 (19-21)	26 (19-46)
Age at diagnosis (months), median (min-max)	8 (1-36)	9 (1-324)
Duration of disease since diagnosis (month), median (min - max)	223 (192-244)	279 (60-492)
Hemophilia severity, n(%)		
- Mild hemophilia	0 (0)	5 (8,5)
- Moderate hemophilia	2 (50)	16 (27,1)
- Severe hemophilia	2 (50)	38 (64,4)
BMI (kg/m ²), mean + SD	18,6 + 2,8	21,5 + 3,8
Substitution therapy in the last 1 month (IU), median (min-max)	4047 (0-6020)	2000 (0-7350)
Substitution therapy per kg body weight in the last 1 month (IU/kg), median (min-max)	83,4 (0-114,2)	35,5 (0-126,9)
Substitution therapy in the last 3 month (IU),mean + SD	10872,5 + 7796,9	6632,6 + 4923,3
Substitution therapy per kg body weight in the last 3 months (IU/kg), mean + SD	213,9 + 155,9	113,3 + 83,9
BMD (g/cm ²), median (min-max)	0,900 (0,823-0,949)	1,062 (0,808-1,337)
Physical activity score (HAL score), mean + SD	69,6 + 12,8	71 + 13,4
Clinical arthropathy score (HJHS score), mean + SD	18,7 + 4,4	23,2 + 11,8
Radiologic arthropathy, n (%)		
Significant arthropathy	3 (75)	46 (80,7)
No significant arthropathy	1 (25)	11 (19,3)
HCV infection, n(%)		
Positive	1 (25)	33 (55,9)
Negative	3 (75)	26 (44,1)
HIV infection, n(%)		
Positive	0 (0)	1 (1,6)
Negative	4 (100)	58 (98,4)

DISCUSSION

There are 1,571 hemophilic children and adults in Indonesia. 152 hemophilic adults living in Jabodetabek were listed and 79 of them went to Hematology Oncology Outpatient Clinic of Cipto Mangunkusumo Hospital at least once in the last 6 months. This was the first study of bone density in hemophilic patients in Indonesia.

The median age of subject in the study was 26 years old with range of age between 19-46 years old. This median age complies with the age of peak bone mass and in accordance with the age of subjects in previous studies.^{10,14,21,26,37,38} The eldest was 46 years old, unlike a few studies before with subjects older than 50 years old.^{18,20,21,22,37-39} The age limitation in this study made uniform bone density measurement possible according to the standard of ISCD to prevent bias caused by age.

Most subjects in this study had normal or high BMI with average of 21.4 kg/m² and similar with studies done by Naderi and Mansouritorghabeh.^{14,38}

All subjects had on demand substitution therapy, meaning that factors were given only if bleeding had already happened. Median use of factor VIII in this study subjects was 2000 IU in the last 1 month or roughly around 24000 IU per year. This was larger than average factor VIII use in Indonesia, which was about 17211 IU in 2006.⁴⁰ Median use of factor VIII per

kilogram body weight in this study was 35,5 IU/kg or roughly around 426 IU/kg in one year. This was lower than on demand therapy in Taiwan as reported by Liou et al (median use of factor VIII 1342,1 IU/kg/year) but higher than data in report by Naderi et al from Iran (average use of 28,8 IU/kg/year - 31,1 IU/kg/year).^{38,41} Up to this day, Iran still use on demand therapy for hemophilia.⁴² The dosage in this therapy was 10 times lower compared with the dosage in prophylaxis therapy in study by Khawaji et al (median use of 4106 IU/kg/year).¹⁹

In this study, the proportion of HCV infection was 54%, which was quite big compared with the study done by Khawaji in which he reported a proportion of 26,9%.¹⁹ Other studies done by Wallny et al, Katsarou et al, and Gerstner et al showed bigger proportion of HCV infection than this study.^{9,18,20} The proportion estimated in this study was similar with a study done in Europe.⁴³

There was only a subject with HIV infection (proportion of HIV infection 1,6%). This result was different from other studies reported by Khawaji et al, Linari et al, Wallny et al, Katsarou et al, and Gerstner et al in which the proportion of HIV infection was between 11,5%-40,3%.^{9,18,20,21,37}

In this study, the proportion of decreased bone density in this study was 6.3% and that result was lower from other similar studies done outside of Indonesia and can be seen on

table 5. This difference was possibly caused by difference estimation using Z-score in this study while other studies used T-score. Choosing Z-score in this study was based on several reasons. Z-score was the standard score for males younger than 50 years old according to the ISCD. Z-score also allows objective measurement and it was estimated by comparing bone density of subjects to those in the population, while

T-score was estimated by comparing to density of peak bone mass population. The weakness of using T-score was younger subjects would have lower bone density and prevalence of decreased bone density would become higher.⁷² When adhering to the criteria by WHO, the proportion of osteopenia and osteoporosis was 29,8% and it was similar with previous studies.

Table 5 Decreased bone density in hemophilia

Study and location	Age of subjects	Decreased bone density definition	Decreased bone density proportion	Reference
Wallny et al, Germany (2007)	Average age of 41,4 + 13,1 years old	T-score	43,5% osteopenia, 25,8% osteoporosis ^o	9
Nair et al, India (2007)	Average age of 29,53 + 9,27 years old	T-score	50% osteoporosis ^o	10
Gerstner et al, USA (2009)	Median age of 41,5 years old (18-66)	T-score	43% osteopenia, 27% osteoporosis ^o	18
Mansouritorghabeh et al, Iran (2009)	Average age of 30,57 + 12,18 years old	T-score	35,7% osteoporosis ^o	50
Katsarou et al, Greek (2010)	Median age of 36 (18-60)	T-score	52% osteopenia, 55,6% osteoporosis ^o	20
Khawaji et al, Sweden (2010)	Average age of 30,5 years old	T-score	40% osteopenia ^o	21
Linari et al, Italy (2012)	Median age of 41,5-45,8 years old**	Z-score	Decreased bone density by 23%***	37
Naderi et al, Iran (2012)	Average age of 27,73 + 9,5 years old	T-score	50% osteoporosis, 7,5% osteopenia ^o	38
Anagnostis et al, Greek (2012)	Average age of 45,87 + 15,15 years old	Z-score	Decreased bone density by 26,9%	46
This study	Median age of 26 years old (19-46)	Z-score	Proportion of decreased bone density of 6,3%	-

^oCriteria of osteopenia and osteoporosis using WHO T-score

*The study divided subjects into 2 groups with different mean age

**The study divided subjects into 3 groups with different median age

***Decreased bone density using Z-score < -2

Low proportion of decreased bone density in this study gave new insight in studying bone density of hemophilic patients. This was the second study involving adult hemophilics using standard measurement of bone density. A study done by Linari et al also used Z-score, but subjects with osteopenia had Z-score between -1 and -2 while osteoporosis had Z-score less than -2.³⁷ Its grouping method was also not in accordance to the guidelines from ISCD, in addition to involving subjects older than 50 years old.³⁸

The difference of results between this study and of Linari et al could be caused by a number of factors. Linari et al involved older subjects with the eldest being 73 years old, causing higher proportion of decreased bone density. Another reason could be the location of study, since Europe as Linari's study place had different race and sunlight exposure while Johnell et al reported that every 10° away from equator increased the risk of osteoporosis as much as 0,6%.⁴⁵

Another study done by Anagnostis et al in Greece in 2012 used bone density measurement in accordance to the standard and reported decreased bone density in 26.9% of their subjects.⁴⁶ But its limitation was involving subjects older than 50 years old with the eldest being 76 years old.⁴⁶ The characteristics of subjects with decreased bone density in this study also different than its predecessor because they were younger with lower BMI compared with studies by Gerstner et al and Naderi et al.^{18,38} They also had lower incidence of HCV and HIV infection compared with Gerstner's report.¹⁸ Substitution therapy was higher compared with osteopenic subjects in Naderi's report (83,4 IU/kg in 1 month vs 31,1 IU/kg in 1 year).³⁸ These differences in characteristics contributed to the different proportions of decreased bone density. Although there were differences found in the studies,

it can be concluded that decreasing bone density happens in hemophilia.

In this study, subjects with decreased bone density were younger with more frequent bleeding both similar physical activity scores and better joint scores than normal subjects. These might be because younger age meant good joints. Good joints allow more physical activities which contributed to more bleeding.

There were 10 histories of fractures in 14.3% of subjects involved in the study, and it was similar with Anagnostis (16%) but lower than Gerstner (20%), Gallacher (36,8%), and Khawaji (23,3%).^{7,18,21,46} It was bigger than Nair (12%) though.¹⁰ The difference could not be explained fully since not all studies described their location, the causes of fractures, and physical activity measurement. The fracture location was similar with Gallacher, Khawaji, and Anagnostis, in which most of them happened not on the bone with risk of pathologic fracture.^{18,21,46} Most of the fractures in this study (90%) were traumatic injuries, which explained the reason they happened in subjects with normal bone density. Level of physical activities in subjects with or without fractures was similar (average HAL scores 71,9 + 12,6 vs 65,4 + 16,4), meaning fractures happened were caused by the intensity of trauma. The causes of fractures in this study were different from Anagnostis report because they report 53% of fractures caused by mild trauma.⁴⁶ The difference of proportion of subjects with fragility fracture on this study with studies by Anagnostis et al and Gerstner et al probably because studies by Anagnostis et al. and Gerstner et al included older subjects.^{18,46}

Gerstner et al reported 50% of fractures in subjects with decreased bone density while Anagnostis reported 18%.^{18,46} Based on these and other studies, it seems there is no exact

explanation of decreased bone density in hemophilia as a cause of fracture.

As for significant age gap in this study, a report from Gerstner had different result because his study subjects who had normal bone density were 20 years younger than those with low bone density.¹⁸ Wallny reported that age had negative correlation with BMD, meaning older age had lower *T-score*.⁹ Both of the studies' results were different from this study result. This could be explained by some reasons. Subjects with decreased bone density in this study had lower BMI, which was a risk factor of osteoporosis both in hemophilic and non hemophilic groups. Low BMI is known to correlate with low peak bone mass and contributed to the loss of bone mass.⁴ Wallny reported BMI to had negative correlation with bone density.⁹ Gerstner reported that their subjects with osteoporosis had significant low BMI.¹⁸ The relationship between low BMI with hemophilic population was confirmed in a metaanalysis.¹¹

Another reason was subjects with decreased bone density used substitutional therapy twice as much as in normal subjects. Indonesia had on-demand therapy in hemophilia, so therapy could be assumed to represent bleeding incidents. This meant subjects with decreased bone density had more bleeding. This study also showed that duration of disease since diagnosis in subjects with low bone density was short, so it seemed that bleeding played more important roles in decreasing bone density in hemophilia. Result of this study also in accordance to the study by Naderi and colleague in Iran which showed that bleeding episodes are significantly more frequent in subjects with osteopenia or osteoporosis.³⁸ Results from this study and study by Naderi et al.³⁸ and also Liel et al.³⁵ suggests that there might be an association between bleeding and reduced bone density. However we still can not rule out that more bleeding in subjects with reduced bone density in this study is merely a consequence of the severity of hemophilia because all subjects with reduced bone density in this study were subjects with severe hemophilia. The association of bleeding and bone metabolism in hemophilia patients still needs further studies to confirm the causal association.

In this study, there was no difference of physical activity level between both groups, similar to a study by Khawaji in 2009, but different from Gerstner who reported better physical activity in normal BMD and Anagnostis who reported positive correlation between physical activity score and bone density.^{18,19,46} In Gerstner and Anagnostis studies, there was no explanation about bleeding frequency or substitutional therapy. Khawaji in 2010 reported significant correlation between duration and the intensity of physical activities with bone density, but this could only be applied to heavy activities and not related to total activities.²¹ This study used HAL score to measure total activities by subjects and caused different results.

Knee arthropathy was also important because it was the most common place for hemarthrosis and had great impact in mobility. The incidence of knee arthropathies was similar in both groups, and this result was different from the result in Anagnostis study.

In this study, HIV infection was lower and found in a

subject with decreased bone density. This was different than the result in studies by Gerstner, Katsarou, and Anagnostis, and it could be caused by the possibility of early diagnosis in those countries since transfusions were done early. This study only had a subject with HIV (1,6%), compared with Gerstner (37%), Anagnostis (38.9%), and Katsarou (6,7%).^{18,20,46} A possible explanation for low HIV infection in hemophilia could be because of unmeasured role of cytokine proresorption TNF- α as the base of decreased bone density.

The subjects in this study had lower HCV infection than studies by Wallny, Gerstner, and Anagnostis.^{9,18,46} Nair and Khawaji did not find the relationship between HCV and low bone density.^{10,19} This difference could be caused by different level of liver fibrosis and viral load, which have not been studied.^{28,47}

There were things that have not been studied yet, such as proinflammation cytokine, bone resorption and formation marker, relationship between independent variable and bone density, direct role of factor VIII deficiency to bone density, and pathophysiology of decreased bone density in hemophilia. Considering the role of factor VIII in inhibition of RANKL and its synergic action with OPG, osteoclast activity is needed to be understood in people with factor VIII deficiency. The relationship between factor VIII and osteoclastogenesis also needs to be understood because the main treatment of osteoporosis is bisphosphonate, which inhibits the role of osteoclast.

Other factors in bone metabolism and pathophysiology of decreased bone density are also need to be considered. Gerstner and Anagnostis found an association between bone density with vitamin D in hemophilia.¹⁸ Other studies by Gowda, Anagnostis, and Linari found vitamin D deficiency in majority of hemophilic subjects, both in adults and children.^{37,46,48}

The study limitation was its cross-sectional design, because it could not define the causal relationship between variables. Its descriptive trait also denied any quantification of association between variables. Another limitation in this study was no examination of inhibitor, vitamin D, and bone metabolism done because of the limited fund. Nonetheless, this study points out that reduced bone density actually happened in hemophilia patients although the prevalence probably not as high as previous reports.

CONCLUSION

The proportion of decreased bone density in adult hemophilic subjects was 6.3%, with all of them had hemophilia A. Subjects with decreased bone density were younger, had lower BMI, had more substitution therapy, better arthropathy score, and lower incidence of blood transmitted infection compared with subjects with normal bone density.

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Systemic sclerosis and hyperthyroidism in pregnancy

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Systemic sclerosis (SSc) is a connective tissue disease affecting women of childbearing age at least five times more than men. For a long time, pregnant women with SSc have high morbidity and mortality based on case reports and case series. Therefore, the disease was a contraindication for pregnancy. However, current retrospective studies show that despite of an increased frequency of prematurity and small for gestational age infants, overall maternal and neonatal survival is good. With close monitoring and appropriate therapy, most scleroderma patients can sustain a successful pregnancy.^{1,2}

CASE REPORT

A 38-year-old woman was referred from Kupang, East Nusa Tenggara to rheumatology outpatient clinic because of thickened skin, chronic dry cough, palpitation, and intermittent difficulty in swallowing since 2 years before admission. She had been diagnosed with scleroderma and hyperthyroid. Her medications in Kupang were methylprednisolone 4 mg b.i.d., propylthiouracil 100 mg b.i.d., propranolol 10 mg t.i.d., and amlodipine 5 mg daily. She had been married for 5 years without any history of contraception and pregnancy. Her vital signs were normal. Her pulse rate was 92 beats/min and regular. She had hyperpigmentation and thickening on almost all of her skin. There were also salt and pepper leukoderma (picture 1) and sclerodactyly (picture 2). Her abdomen was slightly distended and she had Raynaud's phenomenon.



Picture 1 Salt and pepper leukoderma



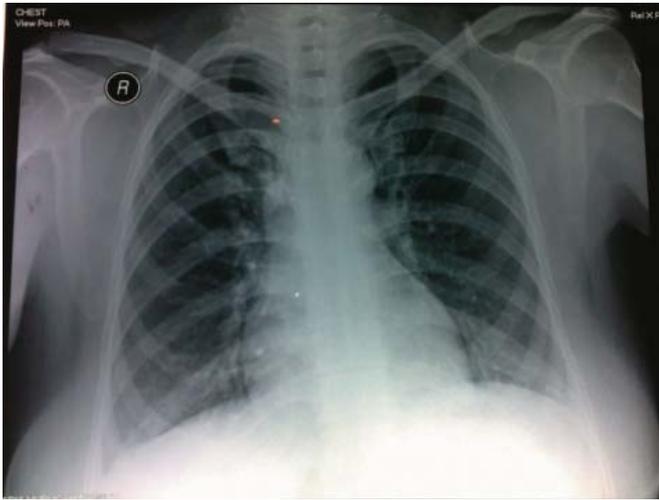
Picture 2 Sclerodactyly

On laboratory examination, we found elevated erythrocyte sedimentation rate (ESR) at 50 mm/hr and leukocytes count of 12.700/mm³. Her urinalysis resulted in elevated protein level at 75 mg/dL. She also had elevated thyroxine (T4) at 27.1 mcg/dL (normal limit: 4.5 – 10.9) and TSHs at 0.09 mU/L (0.35 – 5.5). She was positive for ANA and Anti-Scl-70, but her IgG and IgM anticardiolipin antibody (ACA) were negative. Her echocardiography, esophagogram (picture 3), and chest x-ray (picture 4) were normal. An ultrasound on her thyroid revealed diffuse enlargement with hypoechoic thyroid lobes associated with heterogenous parenchymal appearance.



Picture 3 Barium esophagogram revealed normal esophageal motility (no esophageal dilatation)

An abdominal ultrasound showed a fetus in her uterus with estimated fetal weight of 1100 grams. It was inconsistent with her history of menstruation, because the pregnancy would have been about 31-32 weeks. Her final diagnosis was systemic sclerosis with hyperthyroidism, pregnancy, and intrauterine growth retardation (IUGR). Her



Picture 4 No abnormality detected in the Chest X-Ray

methylprednisolone dosage was changed into once daily in the morning and her propranolol was stopped. She was also consulted to an obstetrician. It was later decided that she was pregnant for 27-28 weeks based on her USG result.

A month later, the patient came with chief complaint of palpitation, diarrhea, and prolonged cough. She was admitted and observed for the possibility of a thyroid crisis. Her vital signs showed blood pressure at 120/ 80 mmHg, heart rate at 122 beats/ minute, respiration rate at 20 times/ minute, and temperature at 36.8 °C. She had normal CBC, renal function test, ECG, and stool examination. Her ESR was at 40 mm/hr and her albumin level was at 2.5 mg/dL. She had elevated thyroxine (T4) at >30 mcg/dL and TSHs at 0.741 mU/L. Her Burch Wartovsky score was 35 (22–44 means impending thyroid crisis). Supportive therapy was given and her conditions improved. She also had monitoring of fetal heart beat every 6 hours and fetomaternal ultrasonography weekly.

Two weeks later, the patient had a fever, cough, and shortness of breath. There were crackles in both lower lobes of her lungs. Her leukocytes count was 12,300/ mm³ and her chest X ray showed honeycomb appearance in lower lobes of her lung. She was diagnosed with pneumonia but interstitial lung disease was thought of as a differential diagnosis. Antibiotic was given for a week. Her conditions improved, but there was a worsening of fetal's non-stress test (NST) and she needed caesarean section. She gave birth to a 1300 grams baby boy with length of 36 cm and Apgar Score 8/9. Five days later, she was discharged from the hospital. The therapy was continued with additional azathioprine 50 mg b.i.d.

Ten days after, the patient was admitted again due to fever and shortness of breath. Her blood pressure was 100/60 mmHg, pulse rate was 92 beats/minute, respiration rate was 28 times/minute, and temperature was 38 °C. Her surgery scar was in good condition. There were crackles in both lower lobes of the lung and her chest x-ray result was the same as before. The laboratory result came back with anemia (8.6 g/dL), low albumin (2.3 mg/dL), normal leukocyte count (9,260/mm³) normal platelet count (233,000/mm³), and elevated ESR (55 mm/hr). Again the patient was diagnosed with pneumonia

and interstitial lung disease as differential diagnosis. Sputum, urine, and blood culture were performed. She was also scheduled for chest high resolution CT scan and pulmonary function test. While waiting for results, she had oxygen 8 L/min, intravenous levofloxacin 750 mg daily, and nebulizer.

A week later, the fever subsided, but her cough and dyspnea worsened. The sputum, urine, and blood culture were all negative. She was then given intravenous cyclophosphamide 500 mg in addition to her ongoing therapy. Three days later, the patient still had dyspnea with increased heart rate (130 times/minute) and respiration rate (39 times/ minute). Her blood gas analysis showed severe hypoxia with type I respiratory failure. There was no chance for assisted ventilation as she suddenly had cardiac arrest and died.

Her baby had neonatal jaundice and sepsis after about 1.5 month in incubator, but with proper treatment he was finally discharged from the hospital without any episode of hypothyroidism.

DISCUSSION

Scleroderma is a connective tissue disease of unknown etiology that afflicts the lungs, heart, gastrointestinal tract, and kidneys. It is a relatively rare disease with an estimated incidence rate ranging from 2 to 10 cases per million. The etiopathogenesis of scleroderma includes vascular dysfunction, mononuclear mediated inflammation, and connective tissue fibrosis.²

Examination for thyroid dysfunction is important in scleroderma as many symptoms of hypothyroidism and hyperthyroidism overlap with scleroderma features. Thyroid fibrosis, autoimmune thyroiditis resulting in hypothyroidism, and hyperthyroidism from Graves' disease are frequent and often unsuspected in scleroderma. Fibrosis of the thyroid gland may develop in the presence or absence of autoimmune thyroiditis. In a Hungarian population, the prevalence of Hashimoto's thyroiditis and Graves' disease was 220-fold higher and 102-fold higher, respectively, in scleroderma patients than in the general population. In particular, anti-thyroid peroxidase (anti-TPO) antibodies are more commonly observed in scleroderma than in controls, and it has been suggested that anti-TPO antibodies may identify the subset of patients at risk for subsequent thyroid dysfunction. It suggests that assessment of thyroid function and anti-TPO antibodies should be done in routine clinical evaluations of patients with scleroderma.^{3,4} In this case, the cause of hyperthyroidism was possibly Grave's disease, because thyroid gland fibrosis usually manifests as hypothyroidism. However, there was no examination of thyroid antibodies due to lack of reagent in the hospital. With anti-thyroid drug (propylthiouracil), she became euthyroid.

Effects of scleroderma on women fertility

The patient had been married for five years without any history of pregnancy and contraception (primary infertility). Her irregular menstrual period could be due to the SSc itself or her hyperthyroidism. The issue of fertility in women with SSc is also difficult to determine because there are many factors, both physical and psychological, affecting pregnancy. Reduced self esteem and altered body image may have great

impact to the ability of patients with scleroderma to form social and sexual relationships. The disease poses further difficulties to interpersonal relationships due to vaginal dryness and dyspareunia which afflicts up to 37% of patients, as well as arthritic involvement and joint contractures which may prevent sexual intercourse. However, there were no specific findings causing infertility that could be attributed specifically to SSc.^{2,5}

Women with scleroderma have twice the rate of spontaneous abortion and three times the rate of infertility (no successful pregnancy up to the age of 35) compared with normal women. The overall rate of a successful pregnancy following a period of infertility was 37% in the scleroderma

patients, similar to the 40% rate in RA patients and 43% in normal controls.²

Effects of scleroderma and hyperthyroidism on pregnancy

The reported outcomes of pregnancy in women with SSc were quite variable. Early literatures were filled with case reports of SSc on pregnancy that resulted in unfavorable outcomes to the mother and/or the baby.⁵ But nowadays close monitoring and appropriate therapy helped scleroderma patients to have a successful pregnancy. In this patient, there were some obstetric complications such as IUGR, premature labor, and the need of emergency caesarean section.^{6,7} As seen in table 1, those three are the most frequent obstetric complications in SSc patients.

Table 1 Pregnancy complications in SSc compared with GOP⁶

	SSc n(%)	GOP* n(%)	P (SSc vs GOP)
Deliveries, n ^o	106	3939	
Intrauterine growth restriction (IUGR) (<5th percentile)	6 (6%)	58 (1%)	p=0,005
Preterm premature rupture of membrane	7 (7%)	126 (3%)	NS
Preterm deliveries <37 weeks	32 (30%)	470 (12%)	p<0,001
Cesarean section	54 (51%)	1222 (31%)	p<0,001
Gestational hypertension	1 (1%)	123 (3%)	NS
Pre-eclampsia/HELLP	1 (1%)	43 (1%)	NS
Eclampsia	0 (0%)	0 (0%)	NS

*GOP: Data from General Obstetric Population followed in 2009 in one of the referral centers

Patients with diffuse skin involvement suffered from more significant morbidities, with premature delivery dominating 40% of pregnancies. Despite all of the possible complications, the overall rate of successful delivery was 84% in limited and 77% in diffuse scleroderma.²

A study for over 12 years involving 60 cases of hyperthyroidism on pregnancy in University Hospital of Wales UK found that metabolic status at delivery correlated with pregnancy outcome. Preterm delivery, perinatal mortality, and maternal heart failure were more common in women who remained thyrotoxic even with clear diagnosis and treatment.⁸ In this patient, she already had hyperthyroidism before her pregnancy and anti-thyroid therapy (PTU) was continued during pregnancy.

Effects of pregnancy on scleroderma and hyperthyroid

In pregnancy, there is an increase of T helper-2, which allows a woman's body to tolerate the fetus, and this is thought to be the reason why the severity of Graves' hyperthyroidism (and other autoimmune diseases) usually lessens after the first trimester⁹. On rare occasions, labour, caesarean section, and infections may aggravate hyperthyroidism into thyroid storm. Most pregnant women with hyperthyroidism have already been diagnosed prior to pregnancy and they tolerate mild to moderate degrees of hyperthyroidism relatively well. Graves

may be exacerbated in the early parts of pregnancy, but as immune suppression typically occurs with the pregnancy, the disease becomes less active. After delivery, they may remain in permanent remission, but recurrence is also possible.^{8,10} In this patient, there was an impending thyroid crisis that could be induced by infection (pneumonia), but she became euthyroid at the end period of pregnancy by using propylthiouracil 100 mg t.i.d. and there was no episode of recurrence postpartum.

Pregnancy appears to exacerbate organs involvement or adversely affect 10 year survival of scleroderma patients. In a prospective series, maternal disease was stable in 60% of cases, improved in 20%, and worsened in another 20%. However, the enlarging gravid uterus may worsen gastroesophageal reflux, which is a prevalent symptom in scleroderma. Likewise, limitation of diaphragmatic breathing may exacerbate pre-pregnancy dyspnea. On the other hand, Raynaud's phenomenon tends to improve in pregnancy due to generalized peripheral vasodilation. Even though pregnancy is not considered to worsen skin disease, progressive skin thickening has been observed in the postpartum women with diffuse disease. As women with diffuse scleroderma are at greater risks for early cardiopulmonary and renal problems, they need to delay pregnancy until their organ functions are stable.² Generally, effects of pregnancy on scleroderma can be seen in table 2 below.⁵

Table 2 Effects of pregnancy on systemic sclerosis

SSc involvement	Changes during pregnancy
General	Stable
Raynaud's phenomenon	Improved during pregnancy, worsen after/during complicated deliveries
Skin	possibility of onset during pregnancy and progressive involvement in postpartum with diffuse SSc
Joints	arthralgia, similar to pregnant women without scleroderma
Gastrointestinal	reflux, similar to pregnant women without scleroderma
Cardiopulmonary	Worsening shortness of breath and should be managed as in any pregnancy with compromised cardiopulmonary status
Kidney	Renal crisis occurs during early diffuse scleroderma with or without pregnancy. Should be managed with ACE-inhibitors despite the fetal risks

Pregnant women with scleroderma are at high risks because of their possibility of having premature delivery and other maternal complications, most notably scleroderma renal crisis (SRC). Initial risk assessment should include disease grading, as women with diffuse disease are at higher risk for miscarriage, preterm delivery, and SRC.²

Management of scleroderma and hyperthyroidism in pregnancy

Management of scleroderma patients during pregnancy, labor, and delivery can be seen in the table 3 below.⁵

Table 3 Management of scleroderma patients during pregnancy, labor, and delivery⁵

Preterm
1. Early evaluation of the extent of organ involvement and autoantibody analysis, including echocardiogram and pulmonary function if necessary
2. Discontinue the use of disease-remitting drugs with teratogenic potential (i.e., MMF, methotrexate, etc.) before pregnancy
3. High-risk obstetric care
4. Reassurance to the mother
5. Minimal use of proton pump inhibitors, histamine antagonist, or calcium-channel blockers for gastrointestinal and vascular problems
6. Avoidance of corticosteroids
7. frequent monitoring of fetal size and uterine activity
8. Frequent blood pressure monitoring
9. Aggressive treatment of hypertension
10. Close observation and treatment for premature labor (avoid beta-adrenergic agonists)
Labor and delivery
1. Epidural anesthesia is preferred
2. Warming of delivery room, intravenous fluid, and the patients themselves (e.g., extra blankets, thermal socks, gloves)
3. Venous access before delivery
4. Careful attention to the episiotomy and incisions, which generally heal without difficulty
Post delivery
1. Continue careful monitoring postpartum, with early reinstatement of medication and aggressive treatment of hypertension

There is no data regarding the preferred method of delivery in scleroderma patients and the decision should be made based on a joint consultation of the inter-disciplinary team. When there is no fetal distress, pulmonary, cardiac, or renal involvement and the patients have good range of motion of hip joints, vaginal delivery is the better choice. One should also keep in mind that severe restrictive lung disease may exist in patients without alveolitis due to established lung fibrosis as well as chest-wall involvement. Performing pulmonary function tests during the first trimester, and if needed, repeating them in later stages of pregnancy, is advisable. The presence of major organ involvement or severe musculoskeletal restriction may emerge the need to have cesarean section.² In this case; the indication of cesarean section was fetal distress.

When organs are severely damaged, such as in cases of severe cardiomyopathy (ejection fraction <30%), pulmonary hypertension, severe restrictive lung disease (forced vital capacity <50%), malabsorption, or renal insufficiency, the decision to terminate the pregnancy may have to be considered depending on the risks to the mother and the fetus.⁵ In this case, her heart and kidney were normal and there was no sign of scleroderma renal crisis. Unfortunately, there was no chance to perform chest HRCT and pulmonary function test. The dyspnea worsened 10 days after delivery and she had been given intravenous cyclophosphamide, but it did not help (maybe too late), she got respiratory failure and died.

Interstitial lung disease (ILD) is a common manifestation of SSc and mainly encountered in patients with diffuse disease and/or anti-topoisomerase 1 antibodies. ILD is now the major cause of mortality in patients with SSC after dramatic reduction in death caused by scleroderma renal crisis, because of the regular use of ACE inhibitors. Although it is important to treat ILD in SSc early, but progression of lung involvement may be variable and difficult to predict. ILD develops in up to 75% of patients with SSc overall. However, SSc-ILD evolves to end-stage respiratory insufficiency in only a few patients. Initial pulmonary function tests (PFT) with measurement of carbon monoxide diffusing capacity, together with HRCT, allows for early diagnosis of SSc-ILD, before the occurrence of dyspnea.^{11,12} This patient had a diffuse disease and her anti-topoisomerase 1 antibodies (Anti-Scl-70) was also positive, making her prone to have ILD. The progress of the ILD was quite fast. In a week she had become worse, fell into respiratory failure despite of intravenous cyclophosphamide.

SUMMARY

This is a case report about a pregnant woman with scleroderma and hyperthyroidism. There were some obstetric complications such as IUGR, premature labor, and the need of emergency cesarean section, but the pregnancy was ended successfully. Unfortunately 10 days after delivery she was admitted again into the hospital due to rapid progressive ILD. Although intravenous cyclophosphamide had been administered, she fell into respiratory failure and died. After about 1.5 month of care in NICU due to low body weight, neonatal jaundice, and sepsis, the baby was discharged without significant abnormality.

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Erosive polyarthritis in multicentric reticulohistiocytosis mimics rheumatoid arthritis

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Multicentric reticulohistiocytosis (MRH) is a very rare multisystemic syndrome.^{1,2} The first case of MRH was described by Goltz and Layman in 1954 and so far only less than 200 cases have been reported.³⁻⁵ It is characterized by the insidious onset of polyarthritis that often evolves into a severe erosive deforming arthritis and characteristic skin lesions composed of nodules and plaques containing lipid-laden (periodic acid-Schiff-positive) histiocytes and multinucleated giant cells.⁶ It most commonly affects the hands and cervical spine.⁷ MRH is also known as lipid dermatoarthritis, lipid rheumatism, and giant cell reticulohistiocytosis.⁴ MRH is caused due to infiltration of multinucleated giant cells and histiocytes into various tissues. The typical pictures include skin nodules and destructive polyarthritis.³ This entity is frequently mistaken for rheumatoid arthritis (RA).³ MRH is often associated with systemic complication and various types of malignancy. Therefore, sometimes it is considered a paraneoplastic syndrome.⁸

CASE REPORT

A 26 year-old Javanese woman was admitted due to abdominal pain since three days before admission. The pain was described as sharp like being stabbed and continuous. She suffered from cough with whitish sputum and sometimes accompanied with shortness of breath in the last two months. She also had decreased body weight for the last two years. The patient was diagnosed with RA since two years ago due to pain, swelling and stiffness on her hand joints, arms, and shoulder joints symmetrically. She was treated with weekly oral dose of methotrexate and low dose methylprednisolone. Patient had been married for seven years and had a three year old child. Recently she had three painless lumps on her back which was not enlarged and sometimes would become reddish.

Physical examination showed she was underweight (body mass index 13,3 kg/m²), tachypnea (respiratory rate 24 x/min), had pale conjunctiva and thin hair. She also had soft mobile painless nodules on her back (figure 1). Abdominal examination revealed hepatomegaly with liver span 18 cm, blunt margin, smooth surface, pain on palpation, and splenomegaly with Schuffner 2. Joint examination showed swollen and tender joint on proximal interphalangeal (PIP) joint I-V and

metacarpophalangeal (MCP) joint I-V bilaterally (figure 2). There was tenderness on elbows, knees, shoulders, and hips.



Figure 1 Lumps on the patient's back



Figure 2 Symmetric polyarthritis on both hands.

Laboratory results showed leukocyte count 11.800/ μ l, hemoglobin level 5.6 g/dl, MCV 81 fl, MCH 27.0 pg, hematocrite 16.8%, thrombocyte count 104,000/ μ l, random blood glucose 137 mg/dl, urea 46.0 mg/dl, creatinine 0.80 mg/dl, SGOT 46 mU/ml, SGPT 15 mU/ml, serum sodium 133 mmol/l, serum potassium 3.72 mmol/l, serum chloride 112 mmol/l. Urinalysis showed leukocyturia 2+, positive nitrite, proteinuria 2+, erythrocyturia 4+, and granule sedimentation in urine 3-5. Rheumatoid factor was negative, CRP 6.06 mg/dl, and erythrocyte sedimentation rate 70 mm/hour.

Chest X-ray showed cardiomegaly, batwing infiltrate in both lungs with prominent fissures, blunting on right sinus phrenicocostalis representing lung edema and pleural effusion dextra (figure 3). Hand X-ray showed periarticular osteoporosis at os carpalis, metacarpophalangeal and interphalangeal

joints digiti I – V manus dextra and sinistra. This similar appearance was also shown at distal radius and ulna, with joint narrowing at proximal interphalangeal proximal and digiti II – V distal. There was joint erosion at PIP digiti II – V manus dextra and sinistra and DIP digiti II – IV manus dextra (figure 4). Pedis X-ray showed porotic periarticular metatarsophalangeal and interphalangeal.



Figure 3 Chest x-ray showing cardiomegaly with pulmonary edema and right pleural effusion.



Figure 4 Hand X-ray showing juxta-articular osteoporosis with erosions (red arrow) on PIP joints.

Fine needle aspiration biopsy of the lumps on her back showed necrotic tissue with many polymorphonuclear inflammatory cells and histiocytes with vacuolated cytoplasm (Figure 5).

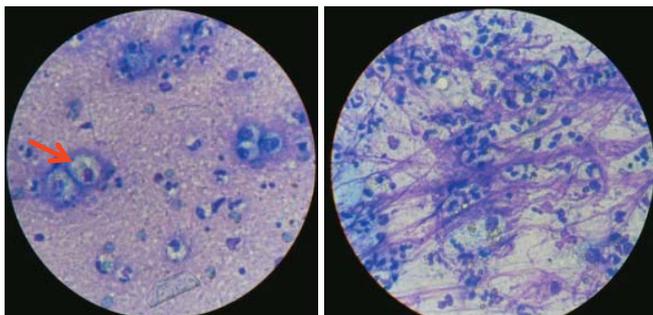


Figure 5 Microscopic finding from the lumps showing histiocytes (red arrow) with vacuolated cytoplasm

Pleural fluid cytology analysis showed malignant cell adenocarcinoma which supported the diagnosis of adenocarcinoma of lung. Finally, patient was diagnosed with multicentric reticulohistiocytosis (MRH) associate with lung malignancy, and she was planned for chemotherapy. Patient passed away due to respiratory failure one month after the diagnosis of MRH was confirmed. She did not have chemotherapy.

DISCUSSION

Multicentric reticulohistiocytosis is a chronic, symmetric inflammatory polyarthritis, most commonly affecting the hands and cervical spine. It may resemble RA,^{9,10} but has prominent distal interphalangeal joint synovitis and can cause a severely deforming arthritis mutilans in 50% cases.^{7,9} Systemic proliferation of multinucleated lipid-laden histiocytes causes swelling in the small joints of the hands and a characteristic erosive pattern on radiographs.¹ A typical ‘string of pearls’ may be seen around the cuticle in some patients.¹ Compared with RA, MRH has the potential to be much more rapidly destructive. Characteristic skin lesions and a negative rheumatoid factor also distinguish MRH from RA.¹¹ Clinical manifestations of MRH and RA are summarized on table 1. The etiology of MRH remains unclear.⁸ The pathophysiology of MRH is not known. A relationship has been made between MRH and infection, malignancy, and autoimmune disease. Such associations suggest that MRH is a reactive inflammatory response with uncontrolled proliferation of the reticulohistiocytes. The strong link with visceral malignancy is consistent with a paraneoplastic process. Most reports support monocytes/ macrophages origin for MRH based on histologic features.⁹

Joint manifestations usually precede nodular skin involvement and many patients have been first misdiagnosed with rheumatoid arthritis.⁹ Two-thirds of patients present with arthritis and skin lesions appear at an average of three years later. About 15-50% progress to mutilating osteoarthropathy and disabling deformities. Some patients have self-limited disease with non-deforming arthritis.² In this case, patient already diagnosed with RA for two years then she developed skin nodule. Arthritis in this patient was also disabling, deforming, without mutilating osteoarthropathy.

In 66% of patients, skin lesion and nodules follow the onset of arthritis by months to years. The skin lesions have a diagnostic histology.⁷ This patient was developed skin lesion after two years of fluctuated arthritis. In 20%, the skin nodules which are firm, flesh-colored to red, brown, or yellow papules are the presenting feature. Pathognomonic lesions are “coral bead” periungual papules, papules on the pinna and vermicular lesions bordering the nostrils.² Skin lesion wax and wane occur around the nailbeds and on the face, extensor surface of the hands and forearms, ears, at mucous membrane and other areas predominantly above the waist.^{7,10} Pink to skin-colored papules that are firm, 2-5 mm in diameter, and often in a linear arrangement are seen in patient with papular mucinosis.¹⁰ On histologic examination, the papules have characteristic giant cells that are not seen in biopsies of rheumatoid nodules.¹⁰

Table 1. Comparison of clinical manifestation between multicentric reticulohistiocytosis (MRH) and rheumatoid arthritis (RA).

Clinical manifestation	MRH	RA
Joint stiffness	Yes*	Yes, typically morning stiffness
Tender and swollen joint	Polyarthritis*	Polyarthritis*
Joint involvement	Hands*, cervical spine. Prominent on DIP* joints	Hands*, wrists, elbows*, shoulders*, knee*, ankle, feet. Rare on spine and DIP joints.
Symmetric joint involvement	Symmetric*	Symmetric*
Nodular skin lesion	Yes, with histiocytes cells on biopsy*	Rheumatoid nodule
Inflammation markers (ESR and CRP)	Increased*	Increased*
Anemia	Mild anemia*	Mild anemia*
Rheumatoid factor	Negative*	Commonly positive
Erosive joint	Yes, prominent on DIP* joints, more progressive erosions	Yes, prominent on carpal bones, MCP and PIP* joints
Juxtaarticular porotic	Yes*	Yes
Association with malignancy	25% Associate with malignancy (breast, stomach, cervix, ovary, colon and lung*	None

*was present on this patient

MRH can spontaneously resolve in 5-10 years, but it can progress to severe arthritis mutilans if not treated.³ There is no effective treatment for MRH. There are several treatment regimens with variable result. The efficacy of these different drug therapies are difficult to assess due to the disease fluctuations and spontaneous remissions.¹¹

All patients diagnosed with MRH should undergo a thorough workup for associated diseases, especially malignancy, because MRH most commonly precede the diagnosis of malignancy. When associated with malignancy, cytotoxic chemotherapy is recommended to control the symptoms of MRH. Non-paraneoplastic cases have been treated with a variety of agents. Nonsteroidal anti-inflammatory agents are not helpful in treating MRH-associated arthropathy. Systemic steroids are palliative, but do not induce remission. Another treatment of MRH consist of variety of medications, including prednisone, methotrexate, cyclosporine, alendronate, zoledronate, and etanercept, and also chlorambucil, and cyclophosphamide.⁹

SUMMARY

A 26 year-old female was diagnosed with multicentric reticulohistiocytosis (MRH) based on symmetric polyarthritis involving PIP, DIP, elbow, shoulder, hip, and knee joints. Joint erosions were identified on PIP and DIP joints, with porotic juxta-articular. Laboratory results showed anemia, increased ESR and CRP levels, and negative rheumatoid factor. Biopsy from skin nodule showed hystiocytes suggestive of MRH. MRH in this patient was associated with lung malignancy and her pleural fluid cytology showed malignant adenocarcinoma cells. She had been misdiagnosed with RA for two years, suggesting that the clinical manifestation of MRH mimics rheumatoid arthritis. MRH should be considered as an important differential diagnosis in patient with erosive symmetric polyarthritis.

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