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Correlation between the level of urine interleukin-6 with microalbuminuria in Systemic Lupus Erythematosus (SLE) patients at Sanglah General Hospital, Bali, Indonesia

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ABSTRACT

Background: Lupus Nephritis (LN) is one of the serious manifestations of SLE. Because of its role in the pathogenesis of LN, IL-6 is likely to be a potential marker, whereas for diagnosing kidney involvement at the subclinical stage, microalbuminuria can be examined. Therefore, early detection of kidney damage in SLE is needed to prevent the progression of NL to permanent kidney failure. This study aims to evaluate the relationship between IL-6 levels and microalbuminuria in SLE patients at Sanglah General Hospital Bali.

Methods: This study used a cross-sectional analytic design, carried out in Sanglah General Hospital on SLE patients, conducted in May until July 2019. Blood and urine samples were taken to obtain the data needed to measure the Mex-SLEDAI score. Cytokine evaluation is done by quantitative examination using enzyme-linked immunosorbent assay (ELISA). Chi-square analysis was done using SPSS version 24 for Windows.

Results: The results of the study were 85 subjects with SLE (94.1% women). The median age is 35 years (18-61 years), and the median duration of illness is three years (0.4-18 years). Most of the patients were in inactive clinical condition, 54 patients (63.53%) and laboratory results were still in the normal range. Steroids (94.1%) are the most widely used therapeutic options. Urine IL-6 levels were obtained with a mean of 0.41±0.21 pg/ml, while microalbuminuria levels were obtained with a median of 20 (0-100) mg/L. The results of data analysis stated that there was no significant relationship between urine IL-6 levels and microalbuminuria in SLE ($p = 0.972$).

Conclusion: In this study, there was no significant relationship between urine IL-6 levels and microalbuminuria.

Keywords: Kidney damage, microalbuminuria, SLE, urine IL-6

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multi-organ disease based on immunological disorders. The manifestations of SLE are diverse, ranging from mild symptoms to severe multi-organ involvement. Lupus nephritis (LN) dominates morbidity and mortality in SLE.[1] In the pathogenesis of LN, cytokines play an essential role, and their balance determines disease activity. In the pathogenesis of SLE, IL-6 plays a dominant role in accelerating the production of autoantibodies by promoting autoreactive B cell proliferation.[2] Local IL-6 expression in glomeruli and tubules has been shown to increase in LN.[3] Because LN causes high morbidity and mortality in SLE patients, it is necessary to have the best screening tool to detect LN events early and prevent the progression of LN to permanent renal failure. Microalbuminuria examination is more sensitive than classical proteinuria to diagnose kidney involvement at the subclinical stage. Dipstick protein examination is most often used as a proteinuria monitoring method because it is comfortable for patients and quickly gets the results of the assessment.[4] Therefore, this study is essential to conduct to know the correlation between urine IL-6 and microalbuminuria in SLE.

METHOD

A a cross-sectional analytic design was conducted in this study at Sanglah General Hospital among 85 SLE patients during May-July 2019. Data were analyzed with the intention to treat principle. All patients with SLE aged 18-60 years who are undergoing treatment at Sanglah Hospital, either through polyclinics or hospitalized, were recruited with consecutive sampling techniques in Sanglah General Hospital Denpasar in 2019.

Subjects with malignancy, sepsis, kidney disease besides lupus nephritis, other autoimmune rheumatic diseases, diabetes mellitus, and lupus nephritis with proteinuria (urine protein>300 mg/day) were excluded. Anthropometric data, laboratory results, and diagnostic data were recorded, which

is needed to measure disease activity based on Mex-SLEDAI scoring. Quantitative examination urine IL-6 is determined by using an enzyme-linked immunosorbent assay (ELISA) method and assessed in pg/mL.

Data processing was performed using Statistical Package for Social Sciences for Windows (SPSS) version 24.0 with $p<0.05$ was significant, and 95% confidence interval.

RESULTS

In this study, as presented in Table 1, there were 85 SLE patients, with most 94.1% females. The median age is 35 years (between 18-60 years), and the median duration of illness is three years (0.4-18 years). The results of laboratory blood tests were relatively no abnormalities were found in this study. Table 2 shows the research data that 31 samples of microalbuminuria were found disease activity in the majority of these samples. While 54 samples were not found disease activity, but the majority of microalbuminuria found in both group samples.

Table 3 shows patient research data that 31 (36.47%) samples with active activity, with more samples found to have urine IL-6 levels >0.42 pg/ml, while 54 (63.53%) samples that with no activity, it was found that more samples had urine IL-6 levels <0.42 pg/ml.

The IL-6 urine cut-off value was obtained based on the ROC curve. In the data presented in Table 4, steroids (94.1%) are the most widely used therapeutic option, followed by other immunosuppressants. From the results of data analysis, it was stated that there was no significant relationship between urine IL-6 levels and microalbuminuria in SLE ($p = 0.972$). Data are presented in Table 5.

Table 1 Clinical characteristics of research subjects

Characteristics	n=85
Sex	
Female	80 (94.1%)
Male	5 (5.9%)
Age (years)	35 (18 – 60)
Duration of disease (years)	3 (0.4 – 18)
Leukocytes (10^3/µL)	7.59 (2.21 – 16.7)
Lymphocytes (10^3/µL)	1.75 ± 0.85
Hemoglobin (g/dL)	12.33 ±1.54
Platelet (10^3/µL)	278.86 ± 73.87
Serum creatinin (mg/dL)	0.67 (0.39 – 1,55)
Erythrocyte sedimentation rate (mm/hour)	27.1 (3.4 - 140)
C-Reactive Protein (mg/dL)	1.45 (0.2 – 114.87)
Urine IL-6 (pg/mL)	0.41 ± 0.21
Microalbuminuria (mg/L)	20 (0 – 100)

IL: interleukin

Table 2 The frequency of microalbuminuria in accordance with the Mex-SLEDAI score

		Mex-SLEDAI Score	
		With activity	No activity
Microalbuminuria	Yes	20 (64.5%)	40 (74.1%)
	No	11 (35.5%)	14 (25.9%)
Total		31 (100%)	54 (100%)

Mex-SLEDAI: Mexican-Systemic Lupus Erythematosus Disease Activity

Table 3 The frequency of urine IL-6 urine in accordance with the Mex SLEDAI score

		Mex-SLEDAI Score	
		With activity	No activity
Urine IL-6	High (>0.42 pg/ml)	18 (58.1%)	25 (46.3%)
	Low (<0.42 pg/ml)	13 (41.9%)	29 (53.7%)
Total		31 (100%)	54 (100%)

IL: interleukin, Mex-SLEDAI: Mexican-Systemic Lupus Erythematosus Disease Activity

DISCUSSION

In this study, the results showed that microalbuminuria occurred in the majority of study samples, both with and without activities assessed based on the Mex-SLEDAI score. In general, activity scores do not correlate with results, but chronicity scores correlate with outcomes, and extra-glomerular lesions are more important than glomerular lesions.[5] Research by Wilhelmus et al. shows that there is ongoing histological activity despite normal urine analysis. It is recommended that repeated renal biopsy be performed not only when glomerular filtration rate decreases but also during fibrosis when proteinuria is not a reliable marker of renal activity.[6]

Study samples with disease activity contained high IL-6 urine (> 0.42 pg/ml) more than low IL-6 urine. On the other hand, in the study sample where no disease activity was found, low urine IL-6 (<0.42 pg/ml) was found compared to high urine IL-6. The results of this study follow some previous studies that showed higher IL-6 urine levels in patients who had disease activity than patients without disease activity.[7-10]

In contrast to previous studies showing a significant relationship between urine IL-6 and microalbuminuria,[9,10] in this study showed no significant relationship between urine IL-6 levels with microalbuminuria in SLE. Similar results were obtained in the studies of Swaak et al., SLE patients may have a normal acute phase response. One hypothesis might be that the disease process (etiology) itself, causes

Table 4 Treatment characteristics of research subjects

Treatment	Yes	No	Total (n=85)
Steroid	80 (94.1%)	5 (5.9%)	85 (100)
Methotrexate	2 (2.4%)	83 (97.6%)	85 (100)
Azathioprine	48 (56.5%)	37 (43.5%)	85 (100)
Cyclophosphamide	5 (5.9%)	80 (94.1%)	85 (100)
Mycophenolate mofetil	6 (7.1%)	79 (92.9%)	85 (100)
Angiotensin II receptor blockers	17 (20%)	68 (80%)	85 (100)
Cyclosporine	4 (4.7%)	81 (95.3%)	85 (100)

Table 5 Pearson correlation analysis results

Variable	Microalbuminuria (mg/L)
Urine IL-6 (pg/mL)	r=-0.004 p=0.972 n=85

r: correlation coefficient; p: probability; n: number of samples

an inhibition of the natural response to injury or the inflammatory process (no IL-6 production), which can determine chronicity and recurrence, or perhaps failure to produce a mediator or mediator that signals hepatocytes to synthesize and excrete acute-phase proteins.[11] Apart from this, the role of IL-6 in the pathogenesis of SLE is also still being debated. This is because the complex cytokine and chemokine environment that influences the differentiation from naive CD4 + T cells to effector CD4 + T cells, including TGF-β, IL-23, IL-21, IL-2, etc.[12]

Several clinical studies have suggested that genetic factors not only determine the tendency to develop SLE but also play a role in developing specific disease phenotypes. It is also known that certain genetic factors are not present in SLE patients, causing an association with a specific phenotype. The production of a specific autoantibody is associated with various manifestations of the disease. It can identify a specific subset in terms of morbidity and mortality and lead to different etiologies.[13,14]

It was also explained based on the time the two variables were measured after undergoing treatment. Urine interleukin 6 is one of the sensitive markers of inflammation, and its level will decrease after treatment.[7,15] In this study all subjects had received a minimum of 4 months treatment so that anti-inflammatory treatment had an effect, proven IL-6 urine in this study ranged from 0.41 ± 0.21 pg/ml below the cut-off value of 4.4 pg / ml.[8]

Weaknesses in this study are the research subjects used are SLE patients who have received treatment. The treatment could affect the measurement of IL-6 urine that has received therapy so that it does not reflect the inflammatory conditions and the timing of IL-6 urine measurements that are less appropriate.

CONCLUSION

In this study, there was no significant relationship between urine IL-6 levels and microalbuminuria in SLE patients.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the manuscript.

ETHICAL CONSIDERATION

This research was conducted based on the ethical conduct of research from the Ethics Committee of the Medical Faculty, Udayana University/Sanglah Hospital Denpasar, and have received permission from the Research and Development Unit (R & D) of Udayana Medical Faculty/Sanglah Hospital.

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AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study from the conceptual framework, data gathering, data analysis, until interpreting the results of the study on publication.

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