Urinary lipoxin A4 as a biomarker for systemic lupus erythematosus

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Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disorder that has multiorgan involvement. The continuation of inflammation in lupus could be attributed to failure of the resolution process because of deficiency of potent endogenous proresolution-inducing molecules such as lipoxin A4 (LXA4), leading to progression and flares of lupus and lupus nephritis.

Objective
The aim of this study was to assess the levels of urinary LXA4 in SLE patients and in healthy controls, and to correlate them with various clinical and laboratory data as well as renal biopsy and disease activity indices (DAIs).

Patients and methods
A total of 40 adult female SLE patients were included in this study. Forty healthy women age-matched with SLE patients served as the control group. All patients were subjected to a full assessment of history, clinical examination, assessment of DAIs (SLEDAI and renal SLEDAI), and laboratory investigations including the urinary LXA4/creatinine ratio assessed by enzyme linked immunosorbent assay.

Results
Urinary LXA4/creatinine ratio levels were found to be significantly higher in all SLE patients compared with the healthy controls ($P = 0.037$). The median level of the urinary LXA4/creatinine ratio was lower in SLE patients with nephritis than in patients without nephritis (0.1 and 0.3 ng/ml, respectively), but with no statistical significance ($P = 0.11$). The urinary LXA4/creatinine ratio levels were found to be significantly lower in SLE patients with cardiovascular manifestations as well as those with neuropsychiatric manifestations ($P = 0.009$, 0.04 respectively).

Conclusion
This was a novel study that was carried out to assess the levels of urinary LXA4 in SLE patients. It showed that the urinary LXA4/creatinine ratio levels were significantly lower in SLE patients with cardiovascular and neuropsychiatric manifestations and nonsignificantly lower in patients with nephritis, suggesting that insufficiency of LXA4 in the human body may be responsible for major organ involvement in SLE patients. Accordingly, LXA4 is suggested to be an inflammatory biomarker not only for lupus nephritis but also for other systemic manifestations in SLE.

Keywords:
activity scores, lupus nephritis, systemic lupus erythematosus, urinary lipoxin A4

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by diverse multisystem involvement and the production of an array of autoantibodies. Clinical features in individual patients can be quite variable, ranging from mild joint and skin involvement to severe life-threatening internal organ disease [1]. The pathogenesis of SLE, which involves the various facets of the immune system, is complex and perplexing [2].

Renal involvement is common in SLE and is a significant cause of morbidity and mortality. It is estimated that up to 90% of SLE patients have pathologic evidence of nephritis on biopsy, but clinically significant nephritis develops in only 50% of patients with SLE. Up to 25% of these patients still develop end-stage renal disease 10 years after the onset of renal compromise. In terms of outcome, the 5- and 10-year renal survival rates of lupus nephritis in the 1990s ranged between 83–93 and 74–84%, respectively [3].

A number of biochemical markers are currently used to clinically assess SLE renal disease activity, such as anti-dsDNA antibodies and complement component levels. Nevertheless, the correlation between these markers and lupus nephritis is imperfect, and their usefulness in reflecting disease activity remains controversial [4]. Thus, novel biomarkers that can discriminate lupus renal activity and its severity, predict renal flares, and

monitor treatment response and disease progress are clearly necessary [3].

Essential ω3 fatty acids, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are precursors to a new genus of potent lipid mediators (LM) that are both proresolving and anti-inflammatory (specialized proresolving mediators) and play a physiologic role defining programmed resolution [5]. Specialized proresolving mediators are endogenously biosynthesized chemical mediators identified in exudates and consist of four distinct new chemical families: lipoxins (LXs), resolvins, protectins, and maresins [6].

LXA4 and LXB4 were the first anti-inflammatory LMs recognized to have proresolving actions. LXs are lipoxygenase interaction products derived from the enzymatic conversion of arachidonic acid by transcellular biosynthesis during cell–cell interactions occurring during inflammation. They act as 'braking signals' of further polymorphonuclear leukocyte infiltration and as potent stimuli for the nonphlogistic recruitment of monocytes and macrophage efferocytosis [7].

Proresolution mediators such as LXs may also have therapeutic potential in settings in which sustained inflammation and impaired resolution are components of disease pathophysiology, thus providing new avenues for the development of treatment strategies and the development of resolution-based pharmacology and lipidomics-based therapeutics [8].

Failure of resolution of inflammation could be the cause of continued inflammatory events observed in lupus, leading to disturbance of the balance between inflammation and resolution more in favor of proinflammatory events and/or failure of resolution. Thus, the healing/repair process is delayed and tissue/organ damage continues [9].

On the basis of this hypothesis, it is suggested that progression and flares of lupus are because of the increased production of proinflammatory molecules interleukin-6 (IL-6), tumor necrosis factor-α, macrophage migration inhibitory factor, high-mobility group box 1, free radicals, and LMs such as prostaglandins, leukotrienes (LTs), and/or decreased formation, and the release of anti-inflammatory molecules: IL-4, IL-10, transforming growth factor-β, and LXs, resolvins, protectins, maresins, and nitrolipids [9].

Objective

The aim of this study was to assess the levels of urinary LXA4 in SLE patients and in healthy controls and to correlate them with various clinical and laboratory data as well as renal biopsy and disease activity indices (DAIs).

Patients and methods

Patients

Forty adult female patients with SLE, diagnosed according to the American College of Rheumatology (ACR) revised criteria for SLE [10], were included in this study as well as 40 healthy age-matched women who served as the control group. SLE patients were conveniently recruited over a period of 1 month on the basis of the following exclusion criteria.

(1) Patients with a diagnosis of overlap syndrome (coexistence of lupus with other connective tissue diseases such as rheumatoid arthritis or scleroderma).
(2) Conditions that could affect the level of LXA4 such as diabetes mellitus, inflammatory lung diseases (e.g. bronchial asthma), and coronary heart disease.

The study was approved by the local ethics committee of Cairo University scientific review board and informed consent was obtained from all participants according to the Declaration of Helsinki; General Assembly, October 2008.

All patients were subjected to the following: full assessment of history, clinical examination, laboratory investigations including erythrocyte sedimentation rate (ESR), complete blood count, liver function tests, kidney function tests, complete urine analysis, 24 h urinary proteins, antinuclear antibodies, anti-dsDNA, C3, and C4 as well as assessment of urinary LXA4, and assessment of disease activity using SLEDAI [11] and the renal SLEDAI [12].

Renal biopsy was performed in patients with established lupus nephritis and the renal pathology was classified according to the revised ISN/RPS system [13].

Assessment of urinary lipoxin A4

Freshly voided urine samples were obtained from all patients and controls and stored at −20°C for later analysis of LXA4 levels using the enzyme linked immunosorbent assay. Measurement of LXA4 in urine samples was performed using an enzyme linked immunosorbent assay kit with product No: EA45,

purchased from Oxford Biomedical Research Inc., USA. LXA4 was extracted from urine samples before analysis using the C18 Sep-Pak® Light Column (Waters® Corporation, #23501; USA) according to the manufacturer's instructions. Urinary creatinine was measured with enzymatic reaction. The results were expressed as the LXA4/creatinine ratio.

Statistical analysis

Statistical analysis was carried out using the Statistical package for social science software, version 15.0, 2006; Echosoft Corporation, Roswell, Georgia, USA. Quantitative parametric data were summarized as mean and SD, whereas nonparametric data were summarized as median and percentiles. Frequency and percentages were used for qualitative variables. Comparison between groups was carried out using the χ^2-test for qualitative variables. One-way analysis of variance and the Kruskal–Wallis test for parametric and nonparametric data, respectively, were used to assess the differences between groups. If significant, post-hoc multiple comparison and Mann–Whitney tests were used to identify exactly where the differences were. The Pearson ranked correlation test and the Spearman ranked correlation test were used for correlation analysis between variables. *P* value was considered significant if less than 0.05.

Results

The 40 adult SLE patients were all women, ranging in age from 18 to 50 years, mean age 29.55 ± 7.7 years, and disease duration ranging from 1 to 20 years, mean 6.99 ± 4.72 years. Forty healthy age-matched women served as the control group; their ages ranged from 18 to 50 years, with a mean of 32.9 ± 10.35 years. The SLE patients were divided into two groups.

Group I included 20 SLE patients without nephritis.

Group II included 20 SLE patients with nephritis, defined as those patients with a renal SLEDAI of 8 or more (at least two abnormal results for renal parameters on at least two occasions).

The pathology of renal biopsy of the SLE patients with nephritis was as follows:

(1) Four (20%) patients were lupus nephritis class II.
(2) Six (30%) patients were class III.
(3) Seven (35%) patients were class IV.
(4) Three (15%) patients were class V.

The results were as follows

There was a significant statistical difference between all SLE patients and the control group in the urinary LXA4/creatinine ratio (P = 0.037) (Tables 1 and 2).

The median level of the urinary LXA4/creatinine ratio was lower in SLE patients with nephritis than patients without nephritis (0.1, 0.3 ng/ml, respectively) and the lowest in the control group (0.058 ng/ml), but with no statistical significance (P = 0.113) (Table 3).

Table 1 Demographic and clinical data of groups I and II SLE patients

Variables	Group I (n = 20) [n (%)]	Group II (n = 20) [n (%)]
Age (years)		
Range	18–40	19–50
Mean ± SD	27.9 ± 5.65	31.2 ± 9.17
Disease duration (years)		
Range	1–20	1–13
Mean ± SD	8.05 ± 5.42	5.93 ± 3.73
Oral ulcers	13 (65)	11 (55)
Malar rash	12 (60)	15 (75)
Discoid rash	1 (5)	2 (10)
Photosensitivity	11 (55)	10 (50)
Alopecia	6 (30)	4 (20)
Arthritis	13 (65)	11 (55)
Myositis	0 (–)	1 (5)
Cardiovascular manifestations	8 (40)	12 (60)
Hypertension	1 (5)	7 (35)
Pulmonary manifestations	14 (70)	12 (60)
Pulmonary hypertension	2 (10)	4 (20)
Neuropsychiatric manifestations	6 (30)	5 (25)
Vasculitic lesions	5 (25)	6 (30)

SLE, systemic lupus erythematosus.

Table 2 Comparison between the 40 SLE patients and the control group in the urinary LXA4/creatinine ratio

Variable	SLE patients (n = 40)	Controls (n = 40)	P value
Urinary LXA4/creatinine ratio (ng/ml)			
Range	0.016–0.38	0.012–2.36	0.037
Median	0.12	0.058	
25th–75th percentile	0.07–0.69	0.03–0.22	

LXA4, lipoxin A4; SLE, systemic lupus erythematosus.

Table 3 Comparison between the median levels of the urinary LXA4/creatinine ratio in groups I and II and the control group

Variables	Group I (n = 20)	Group II (n = 20)	Control (n = 40)	P value
Urinary LXA4/creatinine ratio (ng/ml)				
Range	0.016–0.38	0.02–1.96	0.012–2.36	0.113
Median	0.317	0.11	0.058	
25th–75th percentile	0.05–0.78	0.08–0.66	0.03–0.22	

LXA4, lipoxin A4.

Comparison between SLE patients with and without various clinical manifestations in the urinary LXA4/creatinine ratio showed that its level was significantly lower in SLE patients with cardiovascular manifestations (0.07 ng/ml, $P = 0.009$) as well as those with neuropsychiatric manifestations (0.1 ng/ml, $P = 0.04$) (Table 4).

No statistically significant correlation was found between the urinary LXA4/creatinine ratio and the age ($r = -0.200$, $P = 0.182$) or disease duration ($r = -0.151$, $P = 0.381$) of the SLE patients.

There was a positive significant correlation between the urinary LXA4/creatinine ratio and ESR ($r = 0.432$, $P = 0.008$), but not with other laboratory parameters.

In terms of the level of the urinary LXA4/creatinine ratio, no statistically significant difference was found between SLE patients with positive or negative anti-dsDNA ($P = 0.469$) and between SLE patients with normal or consumed C3 and C4 (0.87 and 0.58, respectively).

There was no significant correlation between the level of the urinary LXA4/creatinine ratio and SLEDAI ($r = 0.299$, $P = 0.076$), or renal SLEDAI ($r = 0.076$, $P = 0.658$) of all SLE patients, as well as the activity scores of the SLE patients when divided into two groups (Table 5).

No statistically significant difference was found between WHO classes of lupus nephritis in SLE patients with nephritis in the urinary LXA4/creatinine ratio ($P = 0.99$) (Table 6).

Discussion

Das [9] proposed that progression and flares of lupus and lupus nephritis are because of the decreased production of LXA4 and enhanced production of LTs by the renal tissue and/or infiltrating leukocytes and macrophages.

In our study, in which we assessed urinary LXA4 in SLE patients and controls, we found that SLE patients had a higher median level of the urinary LXA4/creatinine ratio compared with the control group (0.12 vs. 0.058 ng/ml), with a statistically significant difference ($P = 0.037$). The differential expression of biomarkers in serum and urine of SLE patients may reflect the pathophysiological status of disease development and may therefore be used as biomarkers for early diagnosis and prognosis. Generally, urinary substances are likely to reflect kidney damage better than serum components. Urine is a source of biofluid that is easy to harvest and the biomarkers in urine usually reflect the renal function directly in various kinds of nephritic diseases [14].

It is noteworthy that Wu *et al.* [15], who studied the temporal changes in blood and urinary LXA4, LTB4, and urinary LTE4 in 49 children with Henoch–Schönlein purpura, showed that blood and urinary LXA4 in the active phase (on the day before treatment) were also higher than those of the controls and further increased in early resolution, and this was in contrast to the blood LTB4 and urinary LTB4 and LTE4, which showed an early peak in the active phase and a subsequent decrease during early resolution. This temporal changes between gradually enhanced LXA4 production and gradually suppressed LTB4 and LTE4 generation suggested eicosanoid class switching during acute inflammation and resolution.

Our results showed that the median level of the urinary LXA4/creatinine ratio was lower in SLE patients with nephritis than in patients without nephritis (0.1, 0.3 ng/ml, respectively), but with no statistical significance ($P = 0.113$). This is in agreement with the hypothesis of Das [9], who reported that a deficiency of LXA4 and excess of LTs may be responsible for lupus/lupus nephritis and he proposed that the urinary levels of LXA4 and LTs may be used to predict prognosis and response to treatment. He postulated that if the urinary LXA4 levels revert to normal or are slowly increasing with

Table 4 Comparison between SLE patients with and without various clinical manifestations in the urinary LXA4/creatinine ratio

Variables	Urinary LXA4/creatinine ratio [median (25th–75th percentile)] (ng/ml)		*P* value
	Patients with	Patients without	
Mucocutaneous manifestations	0.12 (0.06–0.66)	0.56 (0.09–1.7)	0.2
Arthritis	0.11 (0.08–0.7)	0.14 (0.05–0.83)	0.83
Myositis	1.96	0.11 (0.06–0.67)	0.13
Cardiovascular manifestations	0.07 (0.04–0.29)	0.47 (0.11–1)	0.009
Pulmonary manifestations	0.11 (0.07–0.81)	0.13 (0.06–0.56)	0.66
Pulmonary hypertension	0.67 (0.1–0.9)	0.11 (0.06–0.65)	0.24
Neuropsychiatric manifestations	0.1 (0.06–0.62)	0.56 (0.29–1.1)	0.04
Vasculitic lesions	0.45 (0.09–0.75)	0.12 (0.06–0.78)	0.42

LXA4, lipoxin A4; SLE, systemic lupus erythematosus.

Table 5 Correlation of the urinary LXA4/creatinine ratio with activity scores in groups I and II SLE patients

Variables	Urinary LXA4/creatinine ratio			
	Group I		Group II	
	r	*P* value	*r*	*P* value
SLEDAI	0.32	0.2	0.33	0.16
Renal SLEDAI	–	–	0.2	0.4

LXA4, lipoxin A4; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.

Table 6 Comparison of urinary LXA4/creatinine ratio levels in WHO classes of lupus nephritis in group II SLE patients

WHO classes of LN	Urinary LXA4/creatinine ratio	
	Median (25th–75th percentile)	*P* value
II	0.12 (0.05–1.3)	
III	0.34 (0.05–0.99)	0.99
IV	0.13 (0.09–1)	
V	0.1 (0.09–0.65)	

LN, lupus nephritis; LXA4, lipoxin A4; SLE, systemic lupus erythematosus.

and without a decrease in urinary levels of LTs, it can be considered an indication that the patient is responding to treatment and that both systemic and renal lesions of lupus are ameliorating.

The urinary LXA4/creatinine ratio levels in our study were found to be lower in SLE patients with cardiovascular and neuropsychiatric manifestations.

The significant relation with cardiovascular manifestations could be compared with the study carried out by Merched *et al.* [16] that tested the hypothesis that atherosclerosis results from a failure in the resolution of local inflammation. Results indicated that 12/15-lipoxygenase expression protects mice against atherosclerosis through its role in the local biosynthesis of LMs, including LXA4, resolvin D1, and protectin D1. These mediators exert potent agonist actions on macrophages and vascular endothelial cells that can control the magnitude of the local inflammatory response. Taken together, these findings suggest that a failure of local endogenous resolution mechanisms may underlie the unremitting inflammation that fuels atherosclerosis.

Indeed, LXs regulate key pathways of vascular hemostasis. Early studies showed LX stimulation of prostacyclin secretion by endothelial cells and vasorelaxant effects, indicating that LXs may regulate the vascular tone. The regulatory effect of aspirin-triggered lipoxin A (ATLa) on nitric oxide release was also reported, although no evidence of a direct impact of LX on nitric oxide biosynthesis has been reported as yet. Consistent with a vasoprotective profile, ATLa inhibited the generation of reactive oxygen species by endothelial cells [17].

Also, Das [18] reported that supplementation of EPA and DHA, respectively suppresses arrhythmias. It is likely that leukocyte and/or myocardial deficiency of EPA and DHA and the consequent reduced formation of LXs, resolvins, protectins, and maresins enhance inflammation and MPO activity, which leads to myocardial damage and fibrosis and initiation and progression of cardiac arrhythmias. On the basis of these evidences, he proposed that LXs, resolvins, and protectins function as endogenous antiarrhythmic molecules and their stable synthetic analogs could be useful in the management of cardiac arrhythmias.

The significant relation with neuropsychiatric manifestations could be explained by the study carried out by Ye *et al.* [19] that showed that the LXA4 analog protects the brain and reduces inflammation in a rat model of focal cerebral ischemia reperfusion. Transient focal cerebral ischemia was induced by middle cerebral artery occlusion for 2 h. Intracerebroventricular administration of the LXA4 analog immediately after the onset of ischemia ameliorated neurological dysfunctions, reduced infarction volume, and attenuated neuronal apoptosis. Moreover, treatment with the LXA4 analog suppressed neutrophils infiltration and lipid peroxidation levels; inhibited the activation of microglia and astrocytes; reduced the expression of proinflammatory cytokines tumor necrosis factor-α and IL-1β; and upregulated the expression of anti-inflammatory cytokines IL-10 and transforming growth factor-β1 in the ischemic brain. These results indicate that treatment of LXA4 analog exerts a strong neuroprotective effect against cerebral ischemia–reperfusion injury, and that these effects might be associated with its anti-inflammatory property.

Yao *et al.* [20] examined the anti-inflammatory effects of ATL in the central nervous system using rat astrocyte cultures stimulated with lipopolysaccharide (LPS). They found that pretreatment with ATL exerted potent anti-inflammatory effects by inhibiting LPS-induced production of nitric oxide and prostaglandin E2 and reduced the expression of cyclooxygenase 2 and inducible nitric oxide synthase mRNA and protein. Furthermore, ATL suppressed the LPS-induced translocation of the NF-κB p65 subunit to the nucleus. These findings suggest that ATL attenuates neuroinflammation by inhibiting the NF-κB signal transducer pathway in cultured cortical astrocytes.

Our results showed that there was a positive significant correlation between the urinary LXA4/creatinine ratio and ESR (r = 0.43, P = 0.008), but not with other laboratory parameters including anti-dsDNA, C3, and C4.

However, in their study of the changes in LXA4 and LTs in children with Henoch–Schönlein purpura, Wu *et al.* [15] showed that with the gradually increased proteinuria, the levels of urinary LXA4 decreased gradually and the levels of urinary LTE4 and LTB4 increased gradually.

Also, Wu *et al.* [21] studied the expressions of 15-lipoxygenase and LXA4 in 22 children with acute poststreptococcal glomerulonephritis, and they reported that the temporal changes in urinary LXA4 and glomerular filtration rate of the patients showed a positive correlation, and the correlation coefficient was 0.528 (P<0.05). However, no significant correlations were found between the temporal changes of urinary LXA4 and the degree of proteinuria, and hematuria of the patients with acute poststreptococcal glomerulonephritis.

Our results showed that there was no significant correlation between the level of the urinary LXA4/creatinine ratio and the activity scores (SLEDAI and renal SLEDAI) of all SLE patients, as well as the activity scores of the two SLE groups. There was no statistical significance in the urinary LXA4/creatinine ratio levels within different WHO classes of lupus nephritis in SLE patients with nephritis.

However, Wu *et al.* [15], who studied the changes in LXA4 and LTs in 22 children with Henoch–Schönlein purpura with nephritis, found that concordant with the gradually increased grade of mesangial proliferation, the levels of urinary LXA4 decreased gradually and urinary LTE4 and LTB4 increased gradually. Correlation analysis between urinary LXA4 and the grade of mesangial proliferation showed a negative correlation, and the correlation coefficient was −0.657 (P < 0.05) in their study.

Conclusion

This was a novel study to assess changes in the levels of urinary LXA4 in SLE patients and to correlate them with various clinical and laboratory data. It showed that the urinary LXA4/creatinine ratio levels were lower in SLE patients with cardiovascular and neuropsychiatric manifestations as well as those with lupus nephritis, suggesting that insufficiency of LXA4 in the human body may be responsible for major organ involvement, making the disease more severe and progressive. Accordingly, LXA4 is suggested to be an inflammatory biomarker not only for lupus nephritis but also for other systemic manifestations in SLE.

We, therefore, recommend that longitudinal studies be carried out with larger number of patients to follow changes in serum and urinary LXA4 levels, and compare their levels with other proinflammatory molecules such as LTs. Furthermore, researchers should evaluate the efficacy of administration of aspirin in SLE patients to induce ATL, which has potent anti-inflammatory properties, and use LXA4 as a therapeutic target in the management of lupus/lupus nephritis.

Acknowledgements

Conflicts of interest

None declared.

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